

Female pelvic floor surgery:

Long-term outcome of the tension-free vaginal tape procedure and the
diagnostic value of occult incontinence testing

PhD thesis

by

Rune Svenningsen, MD

2013

**Department of Gynaecology,
Oslo University Hospital, Ullevål**

and

**University of Oslo,
Faculty of Medicine,
Norway**



**UNIVERSITY
OF OSLO**

TABLE OF CONTENTS

ACKNOWLEDGEMENTS.....	5
LIST OF PAPERS.....	7
ABBREVIATIONS.....	9
SUMMARY.....	11
1. INTRODUCTION.....	15
1.1. The Female Pelvic Floor.....	15
1.2 Urinary Incontinence.....	16
1.3 Surgical management of Urinary Incontinence	18
1.4 Pelvic Organ Prolapse	21
1.5 Pelvic Organ Prolapse surgery.....	24
1.5.1 Stress urinary incontinence on prolapse reduction (Occult incontinence).....	24
1.5.2 Postoperative stress urinary incontinence (POSUI).....	26
1.5.3 The “One-step” or “Two-step” approach to POP surgery?.....	27
1.6 The Norwegian Female Incontinence Registry (NFIR).....	29
2. AIMS OF THE THESIS.....	31
3. MATERIAL AND METHODS.....	33
3.1 Patient selection	33
3.1.1 The TENT study (Papers I and II).....	33
3.1.2 The POSUI study (Paper III).....	34
3.2 The Norwegian Female Incontinence Registry.....	35
3.3 Questionnaire and objective evaluation tools.....	36
3.3.1 Urinary Incontinence.....	36
3.3.2 Pelvic Organ Prolapse.....	42
3.3.3 Occult Incontinence.....	42

3.4 Urodynamic evaluations.....	44
3.5 Outcome measures.....	45
3.5.1 The TENT study (Papers I and II).....	45
3.5.2 The POSUI study (Paper III).....	47
3.6 Statistical analyses and power calculations.....	48
3.7 Legislation and research ethics	50
4. SUMMARY OF RESULTS.....	53
4.1 Paper I.....	53
4.2 Paper II.....	55
4.3 Paper III.....	56
5. GENERAL DISCUSSION.....	59
5.1 Methodological considerations.....	59
5.1.1 Study design and study populations.....	59
5.1.2 Questionnaire.....	61
5.1.3 Occult incontinence testing.....	64
5.1.4 Strengths and limitations.....	66
5.1.5 Statistical analyses.....	72
5.2 Discussion of results.....	75
6. CONCLUSIONS.....	87
7. RECOMMENDATIONS AND CLINICAL PERSPECTIVES.....	89
8. ERRATA.....	91
9. OTHER PUBLICATIONS DURING THE PHD PERIOD.....	93
10. REFERENCE LIST.....	95
11. APPENDICES.....	113
12. PAPERS I-III	121

ACKNOWLEDGEMENTS

The present PhD work was carried out at the Department of Gynaecology, Oslo University Hospital, Ullevål and at the Faculty of Medicine, University of Oslo from 2007 to 2013.

I want to express my sincerest gratitude to my mentor Ellen Borstad who introduced me to the field of urogynaecology. Had it not been for her enthusiasm I would probably never started working in this field. As the former Head of the Urogynaecology Unit, she recruited me to her Unit just months after I started at the Department in 2004 and convinced me that this was the field in which I ought to concentrate my work effort. I am immensely grateful for having been allowed to learn from her vast knowledge in the field and for her patience in the operating theatre perfecting my surgical skills. She has in the 10 years we have worked together been an ever-present monumental example on how to meet all patients with empathy, curiosity and knowledge.

I am also greatly indebted to my main supervisor, Professor Annetine Staff, the Head of the Research Group of Obstetrics and Gynaecology at Oslo University Hospital, for convincing me to go in to research. Her compelling argument that no clinician is complete without at least some knowledge on how to plan, conduct and publish research within his or her field won me over. I am convinced today that undertaking this work has made me a better doctor for my patients. I am forever grateful for her continuous support, her smile and her impressive “superwoman” ability to oversee all her PhD students. She always makes you feel that you are the only one.

I am also grateful to my co-supervisor, Sigurd Kulseng-Hanssen who was the initiator of the TENT-study that forms the greater part of this PhD thesis. During our work with the TENT-study he has taught me the ins and outs of the workings of a national quality registry.

Thanks also to my co-authors Anny Spydslaug, Hjalmar Schiøtz and Kari Western for your considerable part in this thesis by your knowledgeable input and continuous support, and especially Professor Leiv Sandvik who helped me with the statistics.

A special thanks to the system developer Tomislav Dimoski at the National Female Incontinence Registry, whose innovative development of a new application to the National Female Incontinence Registry made this work possible.

I would also like to thank the urotherapists at the hospitals participating in the studies constituting this thesis. Without your positive attitude and hard work in collecting data and evaluating many of the women this would have been an extremely difficult undertaking. A special thanks to the urotechnician at Oslo University Hospital, Øystein Bjørnerud, who has provided invaluable help collecting data and performing urodynamic investigations for this PhD work right from the start in 2007 and all the way to the finish line.

My gratitude also to Bjørn Busund, Head of the Department of Gynaecology and Anny Spydslaug, Head of the Unit for benign gynaecology at Oslo University Hospital for giving me the privilege of holding a combined researcher-clinician position from 2010. Both have, thankfully, always been supportive and held a positive attitude towards my work.

I also want to thank the coordinator of the Research Group of Obstetrics and Gynaecology, Tone Haug, for giving invaluable assistance during the final preparation of the manuscript.

Finally I would thank family and friends for their continuous support and for their unending effort in persuading me that there also is a life to be lived outside the Hospital.

Oslo, March 11th 2014

Rune Svenningsen

LIST OF PAPERS

- I. Svenningsen R, Staff AC, Schiøtz HA, Western K, Kulseng-Hanssen S.**

Long-term follow-up of the retropubic tension-free vaginal tape procedure.

Int Urogynecol J. 2013 Aug; 24(8): 1271-8

- II. Svenningsen R, Staff AC, Schiøtz HA, Western K, Sandvik L, Kulseng-Hanssen S.**

Risk factors for long-term failure of the retropubic tension-free vaginal tape procedure

Neurourol Urodyn. 2013 Aug 14 [Epub ahead of print]

- III. Svenningsen R, Borstad E, Spydslaug AE, Sandvik L, Staff AC.**

Occult incontinence as predictor for postoperative stress urinary incontinence following pelvic organ prolapse surgery.

Int Urogynecol J. 2012 Jul; 23(7): 843-9

Papers I and III are re-printed in this thesis with kind permission from Springer publishing.

Paper II is re-printed in this thesis with kind permission from Wiley-Blackwell publishing.

ABBREVIATIONS

CI	Confidence interval
DOR	Diagnostic odds ratios
FDA	Food and Drug Administration
ICI	International Consultation on Incontinence
ICS	International Continence Society
IIQ-7	Incontinence Impact Questionnaire (short form)
ITT	Intention to treat
IUGA	International Urogynecological Association
LOCF	Last observation carried forward
LR+	Likelihood ratios for positive tests
LR-	Likelihood ratios for negative tests
MUCP	Maximum urethra closure pressure
MUI	Mixed urinary incontinence
NFIR	Norwegian Female Incontinence Registry
NNT	Number needed to treat
NPV	Negative predictive value
OAB	Overactive bladder
OI	Occult incontinence
OR	Odds ratio
P abd	Abdominal pressure
PDFI	Pelvic Floor Distress Inventory
POP	Pelvic organ prolapse
POSUI	Postoperative stress urinary incontinence
PPV	Positive predictive value
P ves	Intravesical pressure
PVR	Post void residual
Q _{max}	Maximum urine flow rate

Qol	Quality of life
ROC	Receiver-operating characteristics
SUI	Stress urinary incontinence
TENT	TEN-year after TVT
TVT	Tension-free vaginal tape
UDI	Urogenital Distress Inventory (short form)
UI	Urinary incontinence
UISS	Urinary Incontinence Severity Score
UUI	Urgency urinary incontinence
UTI	Urinary tract infection
WHO	World Health Organization

SUMMARY

Stress urinary incontinence (SUI) and pelvic organ prolapse (POP) are both manifestations of pelvic floor dysfunction and represent major health problems for the female population. These conditions may affect women as separate or coinciding entities. Both conditions have surgery as a treatment option, and both are diagnosed based on objective findings. However, the decision for using surgical treatment options relies heavily on the patient's subjective symptoms. As surgery is symptom dependent and not based on a life-saving need, the patients should be offered surgical treatment methods that have acceptable long-term outcomes with few complications, few unwanted short- and long-term effects and low re-operation rates.

Retropubic tension-free vaginal tape (TVT) was introduced in 1996 as a new and innovative surgical approach in the treatment of stress urinary incontinence (SUI). The procedure has later also been applied to women with mixed urinary incontinence (MUI) and women with a low-pressure urethra. The short-term results, and short-term complication rates of the TVT procedure have been well documented, but the long-term outcomes for the whole surgically treated population are less known.

De novo postoperative stress urinary incontinence (POSUI) following the repair of pelvic organ prolapse (POP) in previously continent women is a clinical challenge. The exact incidence is unknown, as few non-intervention studies have been conducted. TVT is often used when previously continent women need additional incontinence surgery some time after POP repair due to POSUI. Offering an incontinence procedure only to those that develop POSUI after POP surgery is often referred to as a "two-step" approach. However, the percentage of preoperatively continent POP women needing additional incontinence surgery after POP repair is largely unknown. Performing a "one-step" approach in which TVT is added as a prophylactic procedure to continent women undergoing POP surgery is advocated by some

surgeons, but remains controversial. The extra procedure has the risk of adding greater morbidity to the patient than the condition it is meant to prevent. For that reason, some surgeons have recommended a “selective one-step” approach. By this approach, TVT is added as a prophylactic anti-incontinence procedure only to women believed to have an increased risk of POSUI. Selecting these high-risk women is based on occult incontinence (OI) being diagnosed before surgery. Preoperative diagnosed OI has long been accepted as a predictor (or test marker) for identifying continent women at risk of POSUI. OI is clinically diagnosed when a continent woman with POP displays stress urinary leakage on provocation testing that mimics the POP repair. Using OI as a risk marker is based on the assumption that there is an association between OI and POSUI. This is, however, poorly investigated. There is to date no standardized diagnostic criteria for OI, which possibly explains the large variations in the reported prevalence with different test methods. The diagnostic accuracy and true predictive value of OI as a predictor of POSUI is therefore mostly unknown.

The main aims of this PhD thesis were as follows. First we aimed at revealing the true long-term (10-year) efficacy of the TVT procedure for all patients undergoing the procedure (Paper I). We also wanted to explore any differences in TVT failure rates on the basis of individual preoperative and operative clinical factors such as concomitant POP surgery (Paper II). Secondly, we wanted to investigate the association between occult incontinence (OI) and postoperative stress urinary incontinence (POSUI) after POP surgery (Paper III). Lastly, we wanted to evaluate the test-performance of occult incontinence as predictor for individual women later developing POSUI (Paper III).

For evaluating the long-term (10-year) efficacy of the retropubic TVT procedure, we invited all women, still alive (n=542), that had been operated with the procedure in 1998, 1999 and 2000 at 4 gynaecological departments

within the South-Eastern Region of Norway back for a clinical 10-year follow-up consultation (the TENT study). Those unable to attend were asked to undergo a structured telephone interview. The outcome data collected at the 10-year follow-up were merged with the preoperative, operative and 6-12 months follow-up data stored in the Norwegian Female Incontinence Registry (NFIR).

Logistic regression analyses were performed on two separate outcomes (subjective and objective 10-year failure rates) using additional patient data extracted from NFIR.

The potential statistical association between occult incontinence (OI) and postoperative stress urinary incontinence (POSUI) after pelvic organ prolapse surgery, and the diagnostic accuracy (test performance) of OI testing, were evaluated in a prospective non-interventional observational study at the Department of Gynaecology at Oslo University Hospital. In this study 137 continent women with POP were tested for OI before surgery and de novo POSUI after surgery. Four tests and three test combinations for OI were evaluated.

This PhD thesis concludes that:

- Retropubic tension-free vaginal tape has excellent cure rates 10 years after surgery for the total surgically treated population. Objective cure rate after 10 years was 89.9 %, subjective cure rate 76.1 %, and 82.6 % of the patients stated that they were “very satisfied” with their surgery. Only 2.3 % had undergone repeat SUI surgery at the time of follow-up. Subjective voiding difficulties were reported by 22.8 %, the majority describing slow stream or intermittency. Other long-term unfavourable outcomes investigated were rare (Paper I).
- Patient age ≥ 56 years at the time of surgery, mixed incontinence with a severe preoperative component of urgency incontinence symptoms and surgical complications all proved to be independent risk factors for long-term

failure (Paper II). Concomitant POP surgery was not an independent risk factor for long-term failure in this study.

- There is a statistical significant positive association between occult incontinence (OI) and postoperative stress urinary incontinence (POSUI) (Paper III). However, even though this association was seemingly strong for one test and all test combinations with odds ratios (OR) from 6.8 to 9.0, all tests and test combinations investigated showed poor diagnostic accuracy (test performance) predicting the development of POSUI in individual women. We conclude that OI is a poor clinical marker for POSUI and that a “two-step” surgical approach is recommended (Paper III).

The findings of the present PhD thesis will be used to optimize and individualize the patient counselling prior to both TVT and POP surgery. It will give women more accurate and realistic expectations regarding their long-term outcome after TVT surgery based on individual clinical characteristics. It will hopefully reassure continent women with POP contemplating surgical reconstructions that the risk of developing POSUI is low, and for those few developing POSUI there is the possibility for correcting this later on (using a “two-step” surgical approach). As OI does not adequately identify women who would benefit from prophylactic anti-incontinence surgery at the time of POP surgery, there is currently no medical indication for time-consuming OI testing in ordinary clinical practice.

1. INTRODUCTION

1.1 The Female Pelvic Floor

The female pelvis is an anatomical and functional unit with many tasks beyond the mere support of pelvic organs. It comprises the bony pelvis, striated and smooth muscle fibres, connective tissues, nerves and vascular networks. These components integrate and play vital roles in the healthy normal pelvis. The striated muscular complex, called the levator ani muscle, constitutes (together with the coccygeus muscle) the floor of the pelvis. Standardized anatomical terminology now separates the levator ani muscle complex into three major components: the ileo-coccygeus, the pubo-coccygeus and the pubo-rectalis muscle (1). As the pubo-coccygeus for the most part inserts its fibers into the walls of the vagina and anorectum, not the coccyx, the term pubo-visceralis is favoured by some to comprise the pubo-coccygeus and the pubo-rectalis muscle (1). The pelvic connective tissues are structured into a fascial sheet (endopelvic fascia) covering the pelvic floor muscles, condensing around the organs and forming ligaments connecting the pelvic organs to the bony pelvis (2;3). Smooth muscle fibres also play a vital role in the maintenance of normal pelvic strength, particularly in the anterior vaginal wall in which they are organised in tight bundles oriented in a circular and longitudinal order (4). A decrease in the overall amount of these fibres into fewer, smaller and disorganized bundles has been associated with anterior compartment pelvic organ prolapse (POP) (4;5). Additionally, the vascular network around the urethra are known to contribute to female continence (6;7).

Disruptions of normal function, called dysfunctions of the female pelvic floor, may affect micturition, defecation and sexual function. It may be due to a decline in mechanical strength or disruptions in the finely tuned functional

interactions between the various components (vascular networks, neuronal reflex pathways, connective tissue, striated and smooth muscles) that constitute the pelvic floor unit. Failure of one or more of these functional and structural elements (following trauma, disease or aging) may in some instances start a chain of events leading to a variety of dysfunctional manifestations. Known factors associated with pelvic floor dysfunctions are muscle trauma (8;9), connective tissue remodelling (10-12), changes in smooth muscle fibres (4;5), changes in the vascular network (6;7) and anatomical modifications due to pelvic floor surgery (13;14).

The two most prevalent dysfunctions of the female pelvis are stress urinary incontinence (SUI) and pelvic organ prolapse (POP). Both are conditions gravely diminishing the quality of life for many women (15;16). Both conditions have surgery as one of the treatment options (further described in sections 1.3 and 1.5). As this surgery is performed due to symptoms and not based on a life-saving need, it is of importance that the surgical treatment options demonstrate acceptable long-term results and fewest possible surgical complications, fewest possible short and long-term unwanted effects and low re-operation rates. The lifetime risk for a woman having to undergo surgery for POP or urinary incontinence (UI) by the age of 80 has been found to be 11 % (17;18).

1.2 Urinary Incontinence

Urinary incontinence (UI) is defined, in the joint terminology report from the International Urogynecological Association (IUGA) and International Continence Society (ICS), as the complaint of any involuntary leakage of urine (19). It may be divided into the main categories of stress urinary incontinence (SUI), mixed urinary incontinence (MUI) and urgency urinary incontinence (UUI). As previously mentioned, treatment of urinary incontinence is symptom

dependent and not based on a life-saving need. Therefore, finding the proper management often needs a further characterization in which not only type of incontinence, but frequency and severity, precipitating factors, social impact, effect on hygiene and quality of life is considered (20).

Urinary leakage is highly prevalent and found to affect one in four women in a large community-based epidemiological Norwegian survey (The Norwegian EPICONT Study) (21). The prevalence and the severity are, in several studies, demonstrated to increase with age (21;22). There seems to be an increase in prevalence unto middle age, before falling a little between 50 and 70 years, after which it again shows a steady increase, except for stress urinary incontinence (SUI) peaking at the time of menopause (21).

Stress urinary incontinence (SUI) is defined by the IUGA/ICS as the complaint of involuntary loss of urine on effort or physical exertion (e.g. sporting activities), or on sneezing or coughing (19). Urodynamic stress incontinence may be noted during filling cystometry, and is then defined as the involuntary leakage of urine associated with increased intra-abdominal pressure, in the absence of a detrusor contraction (19;23). SUI is the most prevalent of the different types of urinary incontinence affecting 10 to 39 % of all women, MUI being the next most common affecting 7.5 to 25 % and isolated UUI affecting only 1-7 %, as reviewed by the 5th International Consultation on Incontinence (24). SUI was found to comprise 50 % of all women with urinary incontinence in the Norwegian EPICONT study surveying Norwegian women between 1995 and 1997, with urgency urinary incontinence (UUI) accounting for 11 % and mixed urinary incontinence (MUI) accounting for 36 % (21). Women with SUI demonstrate, on evaluation, a spectrum of urethral characteristics from a highly mobile urethra with a normal or low urethral closure pressure to an immobile urethra with a normal or low urethral closure pressure.

The risk factors for SUI are older age (21;25), pregnancy (26;27), vaginal delivery (25-27), multiparity (25;28), previous pelvic surgery (13;25), menopausal status (25) and repetitive stress on the pelvic floor from constipation (25), chronic cough (respiratory disease) (25) and obesity (25-27). In the younger women, loss of urethral support due to trauma (vaginal delivery) and sphincter function seem to contribute equally to the cause of SUI, while later in life the declining sphincter function dominates (29).

UII is defined by the IUGA/ICS terminology report as the complaint of involuntary loss of urine associated with urgency (19). It is often part of the overactive bladder syndrome (OAB) defined as urinary urgency, usually accompanied by frequency and nocturia, with (OAB wet) or without (OAB dry) UII, in the absence of urinary tract infection or other obvious pathology (19). OAB can be diagnosed on symptoms alone, but may be supported by the occurrence of involuntary detrusor contractions during a filling cystometry. The prevalence of UII symptoms increases with age (21;30-33).

MUI is the coexistence of stress and urgency urinary incontinence and is defined by the IUGA/ICS terminology report as the complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion or on sneezing or coughing (19). The prevalence of MUI symptoms also increases with age (21;33).

Hereditary genetic factors probably predispose for all incontinence types (34-36). For SUI, there is also a substantial influence of environmental factors such as childbirth, obesity and the process of aging (34).

1.3 Surgical management of Urinary Incontinence

Different surgical procedures as management of Stress Urinary Incontinence (SUI) have been offered to women in the developed world for approximately 100 years. Kelly described the open vesical neck in 1912 and

the successful results from an operation involving plication of the vesical neck (37). In 1949 a new innovative approach focusing on the restoration of the posterior vesico-urethral angle was described, called the Marshall, Marchetti, Krantz operation (38). This again led to a new area brought further by a publication from John Burch in 1961 describing an abdominal procedure, first performed in 1958 (39). He demonstrated that suturing the perivaginal tissue to the arcus tendineus fascia pelvis could restore continence, and explained the results as a restoration of normal position and support to the vesico-urethral segment. He later changed the technique finding the iliopectinal ligament (Cooper's ligament) on the superior ramus of the pubic bone to be a more secure site for suture anchoring.

In order to minimize the surgical trauma, several minimally invasive methods for suspending the vesico-urethral segment of the vagina were developed. These, often referred to as transvaginal needle suspensions or needle urethropexies, involved transvaginal placement of sutures anchoring the suburethral endopelvic fascia to the rectus fascia or pelvic bone. One of these procedures was the Stamey's abdominovaginal needle colposuspension (40;41). Other methods of suspending the vesico-urethral segment of the vagina evolving over the years are the pubovaginal slings, traditionally using autologous fascia obtained from the abdominal rectus fascia or tensor fascia lata (42;43). Also allo- and xenografts have been used as sling material (44). All of these methods, with the exception of the Burch procedure, are presently in little use. The pubovaginal slings are used on rare occasions in some centres, but reserved for the difficult cases of intrinsic sphincter deficiency (particularly without hypermobility), simultaneous urethral reconstruction (diverticulectomy or fistula repair) or in patients who have undergone previously failed synthetic mid-urethral sling procedures, as recently reviewed by Hou (45). The Burch procedure has later been modified to be done by conventional laparoscopy or robot-assisted laparoscopy, but is now replaced by mid-urthral slings in most

urogynaecological centres. Until the mid-urethral slings were introduced in the nineties, the Burch colposuspension was considered the most successful surgery for genuine SUI, although the scientific evidence was weak (46). It was known as the “gold standard” to which all later surgical methods had to be compared. However, the long-term results of the procedure have later been found somewhat disappointing (47).

In 1990 Ulmsten and Petros proposed a new theory called “the integral theory of female urinary incontinence” (48). They built further on the growing amount of evidence pointing towards the importance of supporting the mid-urethra rather than the vesico-urethral junction in the female continence mechanism. “The integral theory” explained both stress and urgency symptoms as deriving from a laxity of the vagina caused by defects within the vaginal wall itself or its supporting structures (ligaments, muscles and their connective tissue insertions) (48;49). Essential to this theory was the understanding that the vagina has two distinct anatomical segments, which are being pulled in opposite directions during straining against a connective tissue structure called the pubo-urethral ligament (48;49). The anterior segment of the vagina, called the “hammock”, contains the lower 2/3 of the urethra with the pubo-urethral ligament and ascends with an angle of 45 degrees to the horizontal. During straining the anterior part of the pubo-visceralis muscle stretches this part of the vagina forwards (1st urethral closure mechanism) whilst at the same time the proximal part of the vagina, the “supralelevator vagina”, with its more horizontal positioning, is being pulled backwards by posterior fibres of the pubo-visceralis muscle (2nd closure mechanism). According to this theory, such a simultaneous movement in opposite directions, resulting in the closing of urethra from behind against the pubo-urethral ligament, is an essential supplement to the sphincteric function in order to maintain continence in the female urethra (48;49). The theory was met with scepticism in the beginning, until the tension-free vaginal tape (TVT) was introduced in 1996 and quickly

produced remarkable results (50). The original tension-free vaginal tape (TVT) is a synthetic mesh sling inserted vaginally and placed retropubically on each side of the urethra through the urogenital diaphragm traversing the space of Retzius to the abdominal skin. This sling then replaces the missing function of the pubo-urethral ligament and provides support to the mid-urethra at times of elevated intra-abdominal pressure (such as cough and straining). In theory, the sling exerts no tension to the urethra at rest (50). This technique has later been modified in several ways, the most noteworthy being the alternative insertion via the trans-obturator opening. The synthetic material currently used by all mid-urethral slings on the market is the monofilament macroporous Type-1 polypropylene.

Mid-urethral slings are regarded as the new “gold standard” in surgical treatment of SUI today (51). It is also increasingly used in the treatment of MUI, especially in women where the MUI is dominated by stress urinary symptoms (52;53), and in patients with a low-pressure urethra (54;55).

1.4 Pelvic Organ Prolapse

Pelvic organ prolapse (POP) is defined, in the joint terminology report from IUGA/ICS, as the descent of one or more of the following vaginal compartments; anterior vaginal wall, posterior vaginal wall, the uterus (cervix) or the apex of the vagina (vaginal vault or cuff scar after hysterectomy) (19). It may entail the descent of bladder, rectum, uterus or a peritoneal sack with or without abdominal content (e.g. small intestines) through the natural opening in the pelvic floor through which the urethra and vagina traverse. The examination of POP is, in Norway, performed with the woman positioned in the semi-lithotomy position, but it may also be performed in the left lateral (Sims), supine or standing position, if this better demonstrates the POP. The

POP should be staged according to the Pelvic Organ Prolapse Quantification (POP-Q) system (19;56).

The POP-Q stages are (19;56):

- Stage 0: No prolapse is demonstrated.
- Stage I: Most distal portion of the prolapse is more than 1 cm above the level of the hymen.
- Stage II: Most distal portion of the prolapse is 1 cm or less proximal to or distal to the plane of the hymen.
- Stage III: The most distal portion of the prolapse is more than 1 cm below the plane of the hymen.
- Stage IV: Complete eversion of the total length of the lower genital tract.

Each of the three vaginal compartments (anterior- mid-and posterior) is staged separately.

The most common symptoms of POP are the complaint of vaginal bulging, increased heaviness, bleeding and discharge, splinting/digitations, sexual dysfunction and low backache (19). The presence of a prolapse should always be considered together with relevant POP symptoms, as treatment is symptom dependent. However, there is not always a clear correlation between subjective symptoms and the objective stage of the prolapse, but a good correlation is more commonly present when the prolapse is at the level of the hymen or beyond (57).

POP is common. The prevalence of POP based on the sensation of a mass bulging into the vagina has been found ranging from 5 % to 10 % as reviewed by the 5th International Consultation on Incontinence (24). However, POP has a much higher prevalence when based solely on anatomical examination regardless of symptoms as demonstrated in a Swedish population of women from 20 to 59 years of age where the overall prevalence of POP was 30.8 % (58). An anterior vaginal compartment prolapse is the most common

form of prolapse followed by prolapse in the posterior compartment as the second most common and a mid-compartment (apical) prolapse as the least common (17;59;60). POP may commonly involve more than one compartment (17;59). Prevalence also seems to be race dependent as two studies have found that Hispanic women have the highest prevalence and African American women the lowest after controlling for multiple other factors (59;61). The surgery rate for Caucasian has also been found higher (3 times) than for African Americans (62). The prevalence has in a cross-sectional study from the US been found to increase with age (63). The lifetime risk of any American woman having to undergo at least one surgery for either POP or UI by the time she is 80 years of age has been estimated to 11 % (17;18). However, in a more recent study by Smith et al, the lifetime risk of undergoing POP surgery alone in Western Australia was reported to be 19 % (64). This might be suggestive of local differences in indications for surgery around the world. The risk of having to undergo POP surgery has, however, uniformly been shown to increase with advancing age (17;62;64;65).

The etiology of POP is poorly understood and probably multi-factorial. The most accepted risk factors are vaginal childbirth (61;66-68), increasing body-mass index (59;60;66;69) and advancing age (59;60;70). Additionally repetitive strain on the pelvic floor due to heavy lifting (71;72), genetic factors (34;73), previous hysterectomy (14;70;74;75), previous POP surgery (70), obstetrics factors such as increasing parity (59;74;76), operative vaginal birth (68;69), being younger at first delivery (69) and even pregnancy itself (although less reliably associated) increase the risk for POP (77;78).

There is seldom severe morbidity associated with POP, when adequately diagnosed and treated, and the surgery is therefore always symptom dependent and rarely based on a life-saving need. However, as POP heavily impacts the quality of life and sexual function for many women (15;79), reconstructive surgical POP repair is offered when conservative treatment has proven

unsuccessful.

1.5 Pelvic Organ Prolapse surgery

Surgical treatment is often offered women with symptomatic pelvic organ prolapse (POP) when pessary treatment or pelvic floor muscle training fails, or the women decline these conservative measures. POP surgery can be reconstructive or obliterative, the latter performed in elderly women without a wish for future vaginal intercourse. Reconstructive POP repair aims to correct the prolapse and thereby relieve the associated symptoms while at the same time maintaining the opportunity for vaginal intercourse. POP surgery can be performed either by the abdominal or the vaginal route. The reconstructive techniques either utilise the patient's own tissues (native tissue repair) or supplement the surgery with meshes made from biologic or synthetic materials. Epidemiologic studies from the United States have shown that the majority of POP surgeries are performed by the vaginal route (17;18;62;80). Since women with symptomatic POP often present themselves with a prolapse in more than one compartment (17;59), the reconstructive surgery typically involves a combination of re-suspension of the anterior, apical or posterior compartments.

1.5.1 Stress urinary incontinence on prolapse reduction (Occult incontinence)

“Stress urinary incontinence on prolapse reduction” is the term currently suggested in the joint IUGA/ICS terminology report for stress urinary incontinence only observed after the reduction of a co-existent prolapse (19). The prolapse patient has otherwise no symptoms or signs of incontinence when the prolapse is present. This phenomenon was previously known by a variety of names such as “occult incontinence”, “latent incontinence”, “masked

incontinence”, “potential incontinence”, “hidden incontinence” and “iatrogenic incontinence”. For reasons further elaborated under section 5.1.2, this thesis uses the term “occult incontinence” (OI). OI is clinically diagnosed when a continent woman with POP displays stress urinary leakage during provocation testing. The provocation tests have the objective of mimicking the result after POP repair. OI has long been thought of as a risk-marker for identifying women at high risk of developing POSUI after POP surgery (81;82). The mechanism(s) by which a prolapse may mask SUI, and why the SUI would reveal itself as OI during preoperative testing and subsequently as POSUI after POP repair, is not fully understood. A kinking of the urethra or a direct compression effect by the descending prolapse are suggested as explanations of how some POP patients maintains continence prior to prolapse reduction (83-85). A correction of the anatomy at testing and after POP surgery is suggested to decrease resistance to the urethra, unmasking an intrinsic sphincter deficiency in some patients, and thereby reveal itself as SUI (86;87).

However, the accuracy of OI as a risk-marker for POSUI is poorly investigated. It has repeatedly been shown that continent women with POP, having no demonstrable occult incontinence, also develops POSUI (false negatives) (88-90), and several studies have also demonstrated that a large proportion of continent POP women with demonstrable occult incontinence never develops POSUI (false positives) (88-90). These findings have been suggested by some to be due to a lack of an optimal OI test today, and when this test is eventually discovered in the future, all patients at risk of developing POSUI will be identified during preoperative OI testing (91).

There is to date no standardisation on how best to test for OI. A multitude of tests are described in the literature differing in mode of prolapse reduction (using pessary, vaginal packing, manual/digital repositioning, forceps, speculum etc), type of provocation/stress (Valsalva, cough, exercise regimens or daily life activities), positioning during testing (supine, standing,

sitting, lithotomy, semi-lithotomy) and bladder volumes during testing (83;84;86-89;92-102).

1.5.2 Postoperative stress urinary incontinence (POSUI)

Performing pelvic organ prolapse (POP) surgery carries with it the risk of permanently changing the patient's bladder function. According to an updated review of randomized controlled trials by the Cochrane Collaboration, new overactive bladder symptoms (OAB) were noted in 12 % and new voiding dysfunction in 9 % following POP surgery (103). However, de novo postoperative stress urinary incontinence (POSUI) is the most controversial of these unwanted effects of POP surgery, as adding a prophylactic anti-incontinence procedure might possibly prevent it. POSUI has, in the literature, a reported incidence ranging from 11- 44 % (89;101;103-105). Although the data are limited and the patient groups may be biased, there seems to be a higher risk of POSUI in women undergoing POP surgery that includes mesh in the anterior vaginal wall, as compared to the native tissue repair techniques, possibly due to an overcorrection of the anterior vaginal wall (106;107). Several studies have demonstrated a reduced risk for POSUI both in women with preoperative OI (88;97;101;102) and in women without preoperative OI (88;101) if a prophylactic anti-incontinence procedure is added to the POP surgery in continent POP women. Furthermore, in a meta-analysis from the Cochrane Collaboration of studies randomising patients with POP and occult incontinence to either POP surgery with prophylactic anti-incontinence surgery or POP surgery alone, a significantly higher rate of POSUI was seen in women who did not receive prophylactic anti-incontinence surgery (43 % vs 19 %) (103).

However, it is of concern that even when an anti-incontinence procedure is used as a prophylactic procedure against POSUI, one in five (19 %) still ends up with the unwanted outcome (POSUI) (103). The occurrence of

POSUI, even after prophylactic anti-incontinence surgery has been performed in OI women, has been demonstrated in several large studies (101;105). Lastly, adding to the scepticism of performing a prophylactic anti-incontinence procedure in prolapse women with OI, comes the potentially increased morbidity from the additional procedure. The added morbidity may include bladder outlet obstructions, bladder perforations, haematomas, de novo OAB symptoms and, if a mid-urethral sling with synthetic mesh is used, vaginal mucosa mesh extrusions (101;108;109).

1.5.3 The “One-step” or “Two-step” approach to POP surgery?

There is today a great debate in the urogynaecological field whether or not concomitant POP and SUI surgery for women with coinciding POP and manifest SUI should be performed. According to a recent update from the Cochrane Collaboration, no clear recommendations can be made from the available clinical evidence (103). The controversy is even greater when considering the use of SUI surgery as a concomitant prophylactic procedure in continent women undergoing POP surgery (91;110). There are different approaches to this question in the literature supporting various strategies, none agreed upon by all clinicians or researchers. Practice vary from those recommending prophylactic anti-incontinence procedure (such as the retropubic TVT) in all patients undergoing surgery for POP (the “one-step” approach) regardless of preoperative continence status (91) to those recommending to perform a prophylactic anti-incontinence procedure in none, but rather wait and see which patients develops SUI symptoms after the POP surgery (the “two-step” approach) (110;111). Others again recommend the use of prophylactic anti-incontinence procedures selectively in POP patients with preoperative occult incontinence (the “selective one-step” approach) (102;112;113).

The main argument for adding a prophylactic anti-incontinence procedure to all women undergoing POP surgery, regardless of their OI status (the “one-step” approach), is first of all that it is a simple algorithm that will not miss any patient at risk for developing POSUI. Surgeons favouring this approach argue that today’s tests for OI has low predictability with a high rate of false positives and false negatives and that the correlation between OI and POSUI is disrupted by an anti-incontinence effect from the POP surgery itself (91). The curative effect of the POP surgery itself, such as an anterior colporrhaphy, is inferior (and mostly abandoned as treatment of manifest SUI) to the current methods of incontinence surgery. POP patients not receiving concomitant incontinence surgery are therefore, in their opinion, “robbed” of the most optimal incontinence procedures available. These surgeons often cite the CARE study, demonstrating a reduced incidence of POSUI in all patients, not only OI women, if a prophylactic anti-incontinence surgery was added to the POP surgery (88). Also, the short-term cost for one rather than two surgical treatments (one vs two hospital stays and one vs two sick-leaves) may be less for the society and the patient.

The surgeons favouring prophylactic anti-incontinence procedures only to continent women with OI (“selective one-step” approach) argue that there is a clear association between OI and POSUI evident from the reduction of POSUI seen when adding prophylactic anti-incontinence procedures to OI women only (102;112;113). Furthermore, a selective approach confines the added risk of unwanted effects from the incontinence procedure to the women most at risk for POSUI. It can also be argued that the direct cost related to the mesh used in the anti-continenence surgery (TVT) would be avoided in a great many woman if the a “selective one-step” surgical approach was used.

The surgeons advocating never to perform prophylactic incontinent surgery to continent POP women at the time of surgery, but to reserve this to women actually developing bothersome POSUI (“two-step” approach) often

use the same argument as those favouring prophylactic incontinent surgery in all women, namely that predicting who will need later surgery for POSUI is an inexact science. This conservative approach has the obvious benefit of guaranteeing that no woman receives an unnecessary procedure since a concomitant POP and TVT operation always carries an added risk (101;109).

However, there seems to be universal agreement among surgeons favouring all three options that preoperative counselling is essential, empowering women to participate in the decision-making considering both risks and benefits. If one is contemplating the use of a prophylactic anti-incontinence procedure when undergoing POP repair, finding the right prophylactic procedure seems essential. This optimal procedure should add as little morbidity as possible to the POP procedure, have good long-term results and few long-term unwanted effects.

Reliable cost-benefit analyses need to be performed regarding the “one-step” approach, “selective one-step” approach or the “two-step” approach as, sadly, not only pure medical arguments impact the decision making for health care providers. Such analyses will differ significantly depending on type of health care system and the socioeconomic situation for the relevant patient group.

1.6 The Norwegian Female Incontinence Registry (NFIR)

The Norwegian Female Incontinence Registry (NFIR) was started as a common database September 1st 1998, to which 23 gynaecologic departments in the beginning reported their preoperative, operative, 6-12 months postoperative and 3 years postoperative data (114). In 2013 the Registry was made a national quality database for female incontinence surgery data. The number of hospitals reporting to the national registry has over the last years been fairly constant around 30. At the present (October 2013), there are 29

departments reporting regularly to the NFIR out of 45 departments performing female incontinence surgeries in Norway. These 29 departments perform 83 % of all female incontinence surgeries in Norway (2012). The number of departments reporting to the NFIR is thought to increase as a consequence of the NFIR being given the role of a national quality registry.

The NFIR operates under the Norwegian law on data protection with licence from the Norwegian Data Inspectorate and the Norwegian Health and Medicines Authority. It requires individual patient consent for the storage of de-identified patient data. It operates within the Norwegian Health Personnel Act § 26 and sends out yearly reports to contributing departments in which both the department and the individual surgeon is compared to a national average on numerous outcome measures (complication rates, patient satisfaction, objective results from postoperative incontinence testing). This way the data is continuously used to monitor, secure and improve the quality of the surgical procedures in addition to represent a great potential for research.

2. AIMS OF THE THESIS

The long-term outcomes for all patients undergoing the retropubic tension-free vaginal tape procedure (TVT) as treatment for stress urinary incontinence (SUI) and mixed urinary incontinence (MUI) are not fully investigated. TVT is a relatively new incontinence procedure first implemented in clinical use in 1996. Whether concomitant POP surgery or other preoperative and operative clinical factors are risk factors for long-term failure is unknown. De novo postoperative stress urinary incontinence (POSUI) has long challenged surgeons performing pelvic organ prolapse (POP) repair regardless of surgical methods or surgical skills. It has been argued that adding a prophylactic anti-incontinence procedure, such as TVT, at the time of POP surgery would be an attractive approach in order to reduce the incidence of POSUI. Occult incontinence (OI) has been used as a test marker for identifying patients with high risk of developing POSUI, but the diagnostic accuracy (test performance) of such testing has not been fully investigated.

The specific aims of this thesis were therefore to:

1. Evaluate the long-term results after retropubic tension-free vaginal tape (TVT) procedure.
2. Investigate potential preoperative and operative risk factors, such as concomitant POP surgery, for long-term failure of the retropubic TVT procedure.
3. Investigate and measure the association between occult incontinence (OI) and postoperative stress urinary incontinence (POSUI) after POP surgery and evaluate the test performance of various tests for OI as predictor for POSUI after POP repair.

3. MATERIAL AND METHODS

3.1 Patient selection

The patients investigated in this PhD thesis consist of two separate patient populations; the ten-year follow-up after tension-free vaginal tape (TENT) study population and the postoperative stress urinary incontinence (POSUI) study population.

3.1.1 The TENT study (Papers I and II)

The women included in the TENT study (10-year follow-up after retropubic TVT procedure) form the basis for Papers I and II and were identified using the Norwegian Female Incontinence Registry (NFIR). This study was a multicentre study conducted at four Norwegian hospitals located in the South-Eastern region of Norway; Oslo University Hospital, Asker and Bærum Hospital, Vestfold Hospital and Østfold Hospital. All patients still alive 10 years after their TVT surgery at these hospitals were invited to a clinical follow-up consultation. Women unable to attend were offered a structured telephone interview. The same short-form urinary incontinence disease-specific questionnaire was used for both categories (see section 3.3) (115). The only inclusion criterion was that they had received a retropubic TVT in the time period September 1st 1998 (after the inception of the NFIR) through the year 2000 at one of the participating hospitals. The only exclusion criterion from the study was the inability to give informed consent due to reduced mental capacity. For the complete overview of recruitment and dropouts of the study participants, please see flowchart (Figure 1) in Paper I.

This non-selected heterogeneous patient population consisted of women having received retropubic TVT either as primary or secondary treatment for SUI or MUI. The population included both women with hypermobility of the

urethra, low urethral closure pressure and women undergoing concomitant POP surgery. The surgeries at one of the participating hospitals (Oslo University Hospital) were performed at two separate locations during the study years (Aker University Hospital and Ullevål University Hospital). However, at the time of the 10-year follow-up, these two gynaecologic departments had been merged and re-located at Oslo University Hospital, location Ullevål. All the tension-free vaginal tapes (TVTs) used during the study years were from the same manufacturer (Ethicon Gynecare). A written informed consent was obtained from all participating women (included women undergoing telephone interview only). The data collected at the 10-year follow-up was merged with individual preoperative, operative and 6-12 months follow-up data previously stored in the NFIR. The NFIR also contains 3-year follow-up data for some patients. A 3-year follow-up is, however, not routinely performed at all participating hospitals and therefore contains a high degree of missing data. We therefore decided not to use these incomplete 3-year data in this study.

To evaluate whether the women operated at the four study hospitals were representative of the national patient group, we compared the study group with the remaining women registered in the NFIR having undergone a TVT operation during the study years at other hospitals (n=747). The following preoperative variables were compared: age at the time of surgery, 24-hour pad-test, pad stress test, post void residual volume (PVR), maximum flow rate (Q_{\max}), maximum urethra closure pressure (MUCP), stress incontinence index scores and urgency incontinence index scores.

3.1.2 The POSUI study (Paper III)

The women included, in the POSUI study, were recruited from one gynaecologic department only; Oslo University Hospital, location Ullevål. When the inclusion of patients for the study was commenced in 2007, Ullevål Hospital was an independent University Hospital. In 2008, however, Ullevål

University Hospital was merged with three other hospitals to form Oslo University Hospital, one of them with a small gynaecological department (The National Hospital, Rikshospitalet). As the study was already ongoing, no women treated for POP at this other location within Oslo University Hospital were included.

All women scheduled for POP repair during a 3-year period (June 2007-June 2010) were assessed at the outpatient clinic for possible study participation. Inclusion criteria were any form of POP that needed surgical treatment. Exclusion criteria were a history of stress or urgency urinary incontinence, objective stress leakage during stress testing (without repositioning the prolapse), detrusor overactivity during urodynamic evaluation, inability to give informed consent and the lack of language skills in Norwegian or English. Women who had urgency without incontinence were allowed into the study. For the complete overview of recruitment and dropouts of the study participants, please see flowchart (Figure 1) in Paper III. Written informed consent was obtained from all participating women.

To evaluate whether women participating in the POSUI study differed from the “average” woman undergoing POP surgery at our Department (selection bias), we did a post study comparison between study-patients and the total patient population undergoing POP surgery at our Department in the same time period. The following three variables were compared: surgical age, stage of prolapse and dominating POP compartment.

3.2 The Norwegian Female Incontinence Registry (NFIR)

Data from the NFIR (see section 1.6) was used in the TENT study (Papers I and II). Ten-year follow-up data after TVT are not normally reported to the NFIR, and since this TENT follow-up study was not conducted at every hospitals reporting to the NFIR, the 10-year data could not be exported and

incorporated directly into the national database (NFIR). The latter would have allowed for a direct comparison with previously stored patient data. Instead, a separate Access database was created by the system developer working at the NFIR for the sole use of the participating TENT study hospitals. This allowed the 10-year data to be exported separately to the NFIR and merged with extracted individual patient data previously stored in the NFIR generating a study-database containing preoperative, operative, 6-12 months follow-up data, 3-year follow-up data and 10-year follow-up data for each participating woman. The funding for this system development was by grants from the Nordic Urogynecologic Association (NUGA), the Norwegian Urodynamic Discussion Group (UDYDIG) and the Norwegian Female Incontinence Registry (NFIR).

3.3 Questionnaire and objective evaluation tools

3.3.1 Urinary Incontinence

All hospital departments reporting to the NFIR use a short-form urinary incontinence disease-specific questionnaire, see Appendix 1 (English) and 2 (Norwegian) (115). This questionnaire has been validated in Norwegian and reports on the type of incontinence, the severity of symptoms and the quality of life (QoL) pre-and postoperatively in women undergoing surgeries for SUI or MUI (115). All the preoperative, operative, 6-12 months follow-up and 3-year follow-up data in the NFIR are based on this questionnaire. This questionnaire allows stratification of patients into stress and mixed incontinence by generating symptoms scores for stress and urgency incontinence symptoms resulting in a stress and urgency incontinence index (see below). Only women with an urgency incontinence index of 0 are regarded as having pure SUI.

Based on this questionnaire (see Appendices 1 and 2), a stress incontinence index score ranging from 0 to 12 is constructed from questions 1,

2 and 3 in the questionnaire and similarly quantifies the degree of stress incontinence symptoms (higher scores represent worse symptoms). The relevant questions and response alternatives from Appendices 1 and 2 are as follows:

Stress incontinence index:

1. Do you leak urine?	<i>Yes</i>	<i>no</i>	<i>not relevant</i>
when you cough	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
when you sneeze	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
when you laugh	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
when you walk up or down in stairs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
when you raise from bed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
when you lift heavy objects	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
during physical activity (running to the catch the bus)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
during sports	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
during intercourse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. How often do you leak urine in relation to physical activity, when you laugh, cough or sneeze?

- ☐ never
- ☐ 1 – 4 times each month
- ☐ 1 – 6 times each week
- ☐ once per day
- ☐ more than once per day

3. How large is the amount of urine you usually leak during physical activity or when you laugh, cough or sneeze?

- ☐ nothing
- ☐ drops / moist underwear
- ☐ dripping / wet underwear
- ☐ running / passes through all your clothes
- ☐ running down your legs or down at the floor

The stress incontinence index score is calculated in the NFIR as follows:

- For question 1: Each “yes” marked by the woman, counts 1 and each “no” or “not relevant” counts 0. The summarised scores from question 1 count in the stress index as follows: A summarised score of 0 is counted as 0. A summarised score of 1-3 is counted as 1. A summarised score of 4-5 is counted as 2. A summarised score of 6-7 is counted as 3. A summarised score of 8-9 is counted as 4. Maximum score is 4 for question 1.
- For questions 2 and 3: The alternatives are counted from top to bottom and gives the scores 0, 1, 2, 3 or 4. Maximum score is 4 for question 2 and 4 for question 3.

The maximum stress index score is 12 (4 + 4 + 4).

Based on this questionnaire (see Appendices 1 and 2), an urgency incontinence index score ranging from 0 to 8 is constructed from questions 4 and 5 in the questionnaire and similarly quantifies the degree of urgency incontinence symptoms (higher scores represent worse symptoms). The relevant questions and response alternatives from Appendices 1 and 2 are as follows:

Urgency incontinence index:

4. How often do you experience sudden and imperious need to void and urinary leakage before you reach the toilet?

- ☐ never
- ☐ 1 – 4 times per month
- ☐ 1 – 6 times per week
- ☐ once per day
- ☐ more than once per day

5. How large is the amount of urine you usually leak when you experience sudden and imperious need to void and urinary leakage

- ☐ nothing
- ☐ drops / moist underwear
- ☐ dripping / wet underwear
- ☐ running / passes through all your clothes
- ☐ running down your legs or down at the floor

The alternatives are counted from top to bottom and gives the scores 0, 1, 2, 3 or 4. The maximum urgency incontinence index score is 8 (4+4).

The quality of life index score ranges from 0 to 16 and is constructed from questions 7, 9, 10 and 12 in the questionnaire (higher scores represent worse quality of life), see Appendices 1 and 2.

Quality of life index:

7. How many incontinence pads do you use?

- ☐ none ☐ 1 – 3 per week ☐ 4 – 6 per week ☐ 1 – 4 per day
- ☐ more than 4 per day

9. How often do you avoid activities (for example a hobby, physical training or going out) because you are afraid of leaking urine?

☐ never ☐ seldom ☐ sometimes ☐ often ☐ always

10. Do you avoid places and situations where you are aware of that a toilet is not easily available?

☐ never ☐ seldom ☐ sometimes ☐ often ☐ always

12. Does your urinary leakage influence

	yes	no	not relevant
your vacation?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
your family life?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
your social life (going out, meeting friends)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
your sleep?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

For the construction of the Quality of life index, the alternatives for the questions 7 and 9-10 count from left toward right and give the scores 0, 1, 2, 3 or 4. For question 12, a “yes” counts 1, whereas “no” or “not relevant” counts 0. The maximum quality of life index is 16 (4+ 4+ 4+ 4).

The same NFIR questionnaire was used for the subjective data in all three papers. For the 10-year follow-up data after TVT (Papers I and II), we added three supplemental questions that were not validated;

1. How would you characterize the effect of the operation on your current leakage situation? (Choices given: “cured”, “better”, “unchanged” or “worse”)
2. Have you had the feeling that it is difficult to empty your bladder after the operation? If yes, please describe in detail.

3. Has it been persistently painful to empty your bladder after the operation?

If the response to question 2 was yes, the patients detailed descriptions were classified using the terminology of voiding symptoms standardized in ICS/IUGA joint report (19) into the following groups: “slow stream or intermittency”, “position-dependent micturition”, “need to immediately re-void”, “the feeling of incomplete bladder emptying”, “straining to void” and “hesitancy”. For this study we also added two response options: “more than one of the above”, and “other” (meaning the answers could not be classified into any of the above).

For reasons elaborated under section 5.1.2, we did not use the Qol index in any of the papers constituting this thesis.

A reproducible cough/jump pad stress test is a routine part of the preoperative evaluation before TVT surgery and is also performed at subsequent follow-ups to quantify stress urinary leakage (116). The results from this test are routinely reported to the NFIR. In order to compare the 10-year TVT data (Papers I and II) with objective leakage data previously stored in the NFIR, this test was also chosen as the objective test at the 10-year follow-up. It consists of pad weighing after 20 jumping jacks on the spot and three forceful coughs in the standing position with a standard 300 ml bladder volume. Women unable to perform the test were asked to do a modified version consisting of 10 coughs in the standing position, with the same bladder volume. The test-retest reliability of this test has been found sound when the leakage is visualized by the investigator (117). We extrapolated the test-retest reliability to be just as good when we allowed the patients to keep their undergarments on and instead verified the leakage by increased pad weight. The results from this test was also compared with the standardized pad stress test recorded in the NFIR as it was hypothesized that it would yield comparable results despite being slightly different tests.

In Paper III we used a visualized cough stress test (cough/Valsalva) in the semi-lithotomy position after retrograde bladder filling with 100 ml (first visit) and then 300 ml (second visit) to diagnose OI, and 300 ml (postoperative visit) to diagnose objective POSUI (see section 3.3.3). There were several reasons not to use the standardized pad stress test in this study, the main being the fact that these patients had no history of incontinence and were submitted to occult incontinence testing only. The standardized test has not normally been used when testing for OI in prolapse patients. Furthermore it was found too time-consuming when different types of barrier tests should be performed at the same visit. On the postoperative visit, we chose to repeat the test in the semi-lithotomy position with 300 ml bladder volume enabling best possible comparison to the preoperative tests. However, women complaining of bothersome symptoms at the postoperative visit and deemed being a potential candidate for surgical SUI treatment were given the full evaluation normally given before incontinence surgery, including a standardized pad stress test (2 women).

3.3.2 Pelvic Organ Prolapse

The assessment of pelvic organ prolapse in the POSUI study (Paper III) was done in the semi-lithotomic position during Valsalva and staged according to the Pelvic Organ Prolapse Quantification (POP-Q) system (23;56).

3.3.3 Occult Incontinence

Occult incontinence (OI) is clinically diagnosed when a continent woman with POP displays stress urinary leakage during provocation testing whilst mimicking POP repair. In this thesis we have kept the term occult incontinence (OI) even though the new term used in the joint report from ICS/IUGA on the terminology for female pelvic floor dysfunction is stress

incontinence on prolapse reduction (19). The reasons for this decision is elaborated under section 5.1.2

In the POSUI study, we decided on four different provocation tests for diagnosing OI. All tests were performed on all women before surgery (Paper III). This was to enable evaluation of the diagnostic accuracy of both single tests and test combinations. Before testing, the bladder was emptied with a urinary catheter and the test volume of saline installed (see below). The women were asked to perform a Valsalva manoeuvre and cough vigorously in the semi-lithotomic position during Tests 1-3. Any visual leakage during either coughing or Valsalva was defined as a positive test. Test 4 was deemed positive if there was any subjective feeling of leakage. Test 3 was performed on a separate visit from Tests 1 and 2 (at the time of the preoperative urodynamic evaluation). Tests 1 through 3 were performed both with and without repositioning the prolapse. If there was visual leakage when tested without repositioning the prolapse, the patients were excluded, even if there was no history of incontinence. OI was diagnosed for the test combinations if there was leakage on minimum one of the tests. The prolapse repositioning methods (barriers) and the bladder test-volumes were as follows:

Test 1: 100 ml bladder volumes.

Prolapse manually (digitally) repositioned by examiner.

Test 2: 100 ml bladder volumes.

A pessary that optimally reduced the prolapse was fitted.

Test 3: 300 ml bladder volumes.

The pessary from Test 2 used.

Test 4:

Continuous use of the pessary from Tests 2 and 3 for a minimum of 1 week.

The test combinations were as follows:

Test combination A (Tests 3 and 4).

Test combination B (Tests 2, 3 and 4).

Test combination C (Tests 1, 2, 3 and 4).

3.4 Urodynamic evaluations

In Paper I the maximum urine flow rate (Q_{\max}) was measured by free (spontaneous – no catheter) uroflowmetry. A catheter or bladder scanner (optional) was used to measure the post-void residual volumes (PVRs). The Q_{\max} and PVRs are measured and continuously reported to the NFIR before surgery and at all subsequent follow-ups. The MUCPs stored in the NFIR and used in Paper II are identically measured at the four study hospitals by using an 8 French (Ch) flexible polyurethane microtip dual sensor microtransducer catheter oriented with the sensors pointing to 3 o'clock and with a bladder volume of 300 ml. The rate of catheter withdrawal is 1 mm/s.

In Paper III, a filling cystometry was performed to exclude patients with detrusor overactivity. An 8 French (Ch) flexible polyurethane microtip microtransducer catheter was placed in the bladder through the urethra and the intravesical pressure (P_{ves}) was measured during filling. The abdominal pressure (P_{abd}) was measured with a 10 French (Ch) intra-rectal balloon catheter. The retrograde filling of the bladder was performed through the microtip catheter at a rate of 25 ml/min. If there were any involuntary detrusor contractions (detrusor overactivity) during the filling-phase, the patients were excluded.

3.5 Outcome measures

3.5.1 The TENT study (Papers I and II)

Primary objective outcomes in Paper I were cure rate, failure rate and re-operation rate. Failure rate was also the objective outcome in Paper II. Cure rate was defined as no increase in pad weight (0 g) during a cough/jump pad stress test or the modified version as described in 3.3.1. Failure rate was defined as any increase in pad weight (≥ 1 g) performing these tests or having had repeat surgery for SUI in the 10-year follow-up period. Re-operation rate was defined as any new surgeries for SUI (including periurethral bulking agents).

Primary subjective outcomes in Paper I were treatment satisfaction rate, cure rate, improved rate and failure rate. Failure rate was also used as the subjective outcome in Paper II. Treatment satisfaction rate was defined as the number of patients stating “very satisfied” when given the following choices in the validated questionnaire: “very satisfied”, “moderately satisfied”, “neither satisfied nor dissatisfied”, moderately dissatisfied, and “very dissatisfied”. Subjective cure rate was defined as the percentage of women answering “cured” on supplemental question 1, improved rate as “cured” or “better” and failure rate as “unchanged” or “worse” when given the choices “cured”, “better”, “unchanged” or “worse”. In Paper II, the criteria for failure was wider, and in this paper failure rate was defined as the percentage of women stating “not cured” (that is the sum of patients stating “better”, “unchanged” or “worse”. Women having undergone repeat SUI surgery (including bulking agents) during the 10-year follow-up was excluded when calculating the subjective outcomes in Paper I due to the risk of recall bias on their original surgery (several subjective outcomes). In Paper II, however, this risk of recall bias was non-existing as the sole subjective outcome was failure rate and the

women having had repeat SUI surgery were therefore summarily classified as failures when calculating failure rates in this paper.

Secondary outcomes in Paper I were complications during or immediately following surgery recorded in the NFIR and any long-term unfavourable outcomes discovered at the 10-year follow-up.

The complications routinely registered in the NFIR are as follows:

- hematomas (> 4 cm)
- superficial infections (defined as local tenderness with redness and/or purulent discharge)
- deep infections (defined as abscess formation with or without sinus tract formation)
- bladder perforations
- urethral injury
- bowel injury
- major vessel injury
- major bleeding (> 500 ml)
- catheterization (> 1 week)
- catheterization (> 1 month)
- postoperative vaginal mesh exposure
- postoperative sling release.

The long-term unfavourable outcomes evaluated at 10-year follow-up included the following:

- the rate of patients with low Q_{\max} (defined as < 15 ml/s).
- PVRs > 100 ml and > 200 ml
- asymptomatic vaginal mesh exposures
- subjective voiding difficulties (calculated from supplemental question 2, see section 3.3.1)

- recurrent urinary tract infections (defined as having received more than three antibiotic treatments over the last 6 months)
- persistent painful voiding (calculated from supplemental question 3, see section 3.3.1)
- de novo urgency incontinence (defined as a woman with no preoperative symptoms of urgency incontinence (urgency incontinence index score = 0) developing postoperative urgency incontinence (urgency incontinence index score > 0 and presently in the need of incontinence pads).

3.5.2 The POSUI study (Paper III)

The primary outcomes in Paper III were the prevalence of occult urinary incontinence (OI) and the incidence of postoperative stress urinary incontinence (POSUI). OI was defined as leakage during provocation testing (Test 1-4), see section 3.3.3. POSUI was defined as new onset of subjective symptoms, regardless of severity, with a stress incontinence index score > 0 (validated questionnaire, see section 3.3.1). The strength of a potential association between these primary outcomes (OI and POSUI) was tested on the population level and expressed as odds ratios (ORs) (see section 3.6). The diagnostic accuracy of OI predicting POSUI on an individual level was tested by the use of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio for a positive result (LR+), likelihood ratio for a negative result (LR-) and diagnostic odds ratio (DOR) (see section 3.6).

The secondary outcomes were the rate of patients needing re-intervention for severe POSUI. Re-intervention was defined as either receiving pelvic floor muscle training or surgical intervention.

3.6 Statistical analyses and power calculations

The calculated outcome data in all papers were done as per protocol analysis. In this thesis categorical data are presented as percentages and continuous data as mean (Paper III) or median (Papers I and II) and range. Differences in dichotomous variables were tested using McNemar's test for paired variables, and Pearson's Chi-Squared test or Fisher's exact test for unpaired variables. Two-sided Fisher's exact test was used when the sample size was either below 20, or below 40 if the expected count was less than 5. Differences between groups were tested using the Mann-Whitney-U test for continuous variables. Differences tested with Pearson's Chi-Squared or Fisher's exact tests were expressed as odds ratios (ORs) with 95 % confidence intervals.

A significance level of 5 % was used in all papers. Uni- and multivariate logistic regression analyses were used for identifying risk factors in Paper II. In these analyses, the strength of an association between a variable and a binary outcome were expressed as odds ratios (ORs) with 95 % confidence intervals (CI) and p-values. The significance level for entering a variable into the multivariate model was set to 0.20. Backwards-stepwise variable selection was then used until all remaining variables had $p < 0.05$. When testing for significant interactions between independent variables, none were found. Receiver-operating characteristics curves (ROCs) were used to find an optimal cut-off for dichotomizing surgical age. The "ideal" cut-off value was the surgical age where both sensitivity and specificity were as high as possible for the outcome. The final multivariate model was found to fulfil both the Hosmer-Lemeshow goodness-of-fit test and a test for colinearity (variance inflation factor < 5).

In Paper III, the Standard for Reporting of Diagnostic Accuracy (STARD) initiative was adhered with the exception of using a reference test, as none

such exists for OI (118). Diagnostic accuracy of tests and test combinations was estimated using sensitivity, specificity, positive predictive values (PPVs), negative predictive values (NPVs), likelihood ratios for positive (LR+) and negative (LR-) results, and diagnostic odds ratios (DORs) with 95 % confidence intervals (CI).

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS-PC), version 15.0 for Papers I and III, and version 19 (IBM SPSS Statistics) for Paper II.

Sensitivity, specificity, PPV, NPV, LR+, LR-, DORs with 95 % CIs were all calculated manually with the exception of the 95 % CIs for LR+ and LR- for which an open online calculator at Centre for Evidence-Based Medicine Toronto was used (119).

No sample-size power calculation was performed for the TENT study (Papers I and II). This study is based on a registry database in which the number of patients that potentially could be included from this database gave us a sample size that, according to our knowledge, far exceeds most other publications having investigated the same aims (10-year outcomes).

A sample-size power calculation was, however, performed before commencing on the POSUI study (Paper III). The rate of a positive preoperative test for occult incontinence was set at 50 % based on published literature up to 2007, reporting a 44-80 % prevalence of occult incontinence in patients with POP (83;84;93-96;99). A 20 % difference in outcome (POSUI) between women with occult incontinence (OI) and women with negative tests was considered to be of clinical significance. We wanted the study to have 80 % test power when the expected outcome (POSUI) in the test positive (OI) and test negative groups were 32 % and 12 % respectively. The latter was based on the Norwegian study by Borstad and Rud, who reported a 22 % incidence of POSUI after traditional Manchester operations (104). Using a free and open-

source calculator for epidemiologic statistics (www.openepi.com), we found that 136 women were needed in the study.

3.7 Legislation and research ethics

In all studies constituting the basis for this PhD thesis, the declaration of Helsinki was respected (120). Approval was given from all department heads and institutional personal data officers at the participating hospitals. The TENT study (Papers I and II) and the POSUI study (Paper III) were both evaluated by The Regional Committee for Medical and Health Research Ethics in South-Eastern Norway. The POSUI study was approved in accordance with the Norwegian Research Ethics Act of June 30th 2006 (renamed the Health Research Act in 2009). The Regional Ethics Committee considered the TENT study to represent a quality assurance measure for a treatment already established and thereby exempt from additional ethical approval beyond the approval from all department heads and institutional personal data officers at the participating hospitals. It was considered to be covered within the Health Personnel Act § 26 and therefore outside the mandate of the Regional Research Ethical Committee system in Norway. We chose to obtain written consent from all women participating in all studies. When giving their consent for the TENT study, participating women also gave their consent to the inclusion of previously stored data in the NFIR. As the NFIR is a national quality database that entails the export of data outside the hospitals in which treatment was given, a signed consent form is always obtained from the women at the time of surgery. However, this signed consent does not include the collection of data beyond three years after surgery. It was therefore necessary to obtain additional written consent from women participating in the TENT study in order to merge the 10-year follow-up data with previously stored data in the NFIR.

The POSUI study and the TENT study were both non-intervention studies, and as such not required to be registered in any public trials registry before study start.

Our own ethical evaluation as researchers and clinicians is that both the TENT and the POSUI study represent justified studies that carry the potential of great benefit to the patient groups investigated with no potential risk to any participants, including no violation of sensitive data issues.

4. SUMMARY OF RESULTS

Paper I

Long-term follow-up of the retropubic tension-free vaginal tape procedure

In this prospective observational study, we investigated the surgical outcomes of 483 women from an original cohort of 603 women that had been treated with the retropubic TVT procedure at the study hospitals. These 483 women represented 89 % of the 542 women still alive 10 years after their surgical procedure. Subjective and objective data were collected from 327 (of 483) patients that attended a clinical 10-year follow-up consultation.

Additional subjective data were collected from the remaining 156 women undergoing a structured telephone interview only. This surgically treated heterogeneous cohort had originally been operated by 21 different surgeons and consisted of women having received TVT as either primary or secondary surgical treatment for SUI or MUI. The cohort included women with urethral hypermobility, low urethral closure pressure as well as those having undergone concomitant POP surgery.

We found that the objective long-term (10-year) cure rate was 89.9 % for the whole heterogeneous cohort and that only 2.3 % of the women had undergone repeat SUI surgery during the 10-year follow-up period. The objective cure rate was identical to the 6-12 months postoperative cure rate (90.2 % vs 89.9 %, $p = 0.86$). The subjective long-term outcomes calculated from the questionnaire were; 76.1 % of the women were cured, 18.0 % better, 3.4 % unchanged and 2.5 % stated a worse situation. A large majority (82.6 %) stated that they were “very satisfied” with their treatment. The study revealed a small but significant decline in the percentage of women stating that they were “very satisfied” with the treatment from the 6-12 months follow-up to the 10-year follow-up (89.1 % vs 82.6 %, $p = 0.006$) despite no change in objective cure rates (as stated above).

There was a total complication rate of 8.7 % recorded at or immediately following surgery, the most frequent being hematomas of more than 4 cm in diameter (2.5 %). Other complications, having occurred with a frequency of 1 % or more, were bladder perforations (1.2 %), catheterization > 1 week (1.7 %), catheterization > 1 month (1.0 %) and postoperative sling release (1.9 %). Of the unfavourable long-term outcomes that were recorded at the 10-year follow-up, significantly more women had maximum flow rates (Q_{\max}) < 15 ml/s (26.7 % vs 11.0 %, $p < 0.001$) and post-void residuals (PVRs) above 100 ml (3.5 % vs 0.3 %, $p = 0.006$) when compared with the preoperative data. None had PVRs above 200. A significant change in PVRs was also noted from the 6-12 months follow-up to the 10-year follow-up (3.5 % vs 0.7 %, $p = 0.039$). The maximum flow rates were, however, highly incomplete registered at the 6-12 months follow-up in the NFIR due to uroflowmetry not routinely being used at all hospitals. The 6-12 months follow-up data concerning the maximum flow rate could therefore not be compared with the 10-year follow-up data.

We found an increase in de novo urgency incontinence from 4.1 % at the 6-12 month follow-up to 14.9 % at the 10-year follow-up among women initially diagnosed with pure SUI ($p = 0.013$). Women stating that they were “very satisfied” 10 years after surgery were also found to have significantly lower median urgency incontinence index scores compared to those not stating “very satisfied” (0 vs 5, $p < 0.001$). Similar results (0 vs 4.5, $p < 0.001$) were also seen comparing women stating they were “cured” after 10-years compared with women stating not “cured” (i.e. “better”, “unchanged” or “worse”).

Subjective voiding difficulties were reported by 22.8 %, the most common among these (43.1 %) being a slow stream or intermittent voiding. The percentage of women stating that they were “very satisfied” with the treatment was, however, similar for the women reporting voiding difficulties and those reporting no such problems (83.2 % vs 82.3 %, $p = 0.84$).

Furthermore, there were no differences in maximum flow rates ($Q_{\max} < 15$ ml/s) between the groups (27.7 % vs 27.1 %, $p = 0.92$).

Paper II

Risk Factors for Long-Term Failure of the Retropubic Tension-Free Vaginal Tape Procedure

In this study, secondary risk analyses were performed on the 483 patients from Paper I after merging the outcome data with additional individual data previously stored in the NFIR. We used uni- and multivariate logistic regression analysis to investigate potential preoperative and operative risk factors for long-term (10-year) subjective and objective failure in order to optimize preoperative counselling.

Subjective failure rate was calculated from the 483 women that had either attended the 10-year clinical follow-up or undergone the structured telephone interview. The objective long-term failure rate was obtained from the 327 patients that had attended the clinical 10-year follow-up and undergone one of the pad stress tests described under section 3.3.1. The 10-year incidence of failure (absolute risk) for the total cohort was 25.7 % for subjective failure and 10.1 % for objective failure.

We found that age ≥ 56 years at the time of surgery was an independent risk factor for both subjective (OR: 2.15, CI: 1.40-3.30) and objective (OR: 2.81, CI: 1.30-6.09) long-term failure when compared to women < 56 years.

Mixed urinary incontinence (MUI) before surgery, with a severe component of urgency incontinence symptoms (urgency incontinence index score ≥ 5), proved an independent risk factor for subjective (OR: 2.33, CI: 1.27-4.28) long-term failure. MUI was, however, not found to be a risk factor for objective (OR: 1.39, CI: 0.51-3.79) long-term failure. Furthermore, MUI patients with urgency incontinence index below 5 did not show significantly higher subjective failure rates than women diagnosed with pure SUI.

Surgical complications occurring at or immediately following surgery also emerged as an independent risk factor for subjective (OR: 3.02, CI: 1.53-5.95), but not objective (OR: 2.58, CI: 0.94-7.09) long-term failure in the multivariate analysis.

Neither the degree of stress urinary incontinence symptoms before surgery nor the amount of leakage on pad stress testing before surgery proved to be risk factors for long-term failure of the TVT procedure. We were also not able to demonstrate any association between long-term failure and previously POP surgery, low preoperative MUCP or concomitant POP surgery.

Paper III

Occult incontinence as predictor for postoperative stress urinary incontinence following pelvic organ prolapse surgery

In this study we aimed at measuring the statistical association of occult incontinence (stress urinary incontinence on prolapse reduction) in continent women with POP and the risk for developing postoperative stress urinary incontinence (POSUI) after POP surgery. We evaluated the test performance of four different provocation tests for diagnosing occult incontinence alone and in combination and their diagnostic accuracy in predicting POSUI.

Initially there were 204 patients included in the study. However, 47 women had to be excluded at the second visit (during the urodynamic evaluation) due to subjective or objective incontinence that they had originally not reported as it gave them little bother (see flowchart, Figure I in Paper III). As shown by the flowchart, two women were excluded due to lack of compliance, and 15 chose to withdraw from the study after inclusion. Of the 140 patients that completed the study, there were three women lost to follow-up. The final analyses were therefore done per protocol on 137 patients.

The prevalence of occult incontinence (OI) in this cohort, using the information from our four performed tests, varied from 4 % to 19 %. When

combining tests, the prevalence of occult incontinence (positive tests) was found varying from 27 % to 38 %.

The incidence of POSUI was 17 % for the whole surgically treated cohort when defined as subjective incontinence (stress urinary incontinence index score > 0 on the questionnaire, section 3.5.2). When stratified on basis of the preoperatively dominating prolapse compartment, the POSUI incidences were 20 % (anterior compartment), 18 % (mid-compartment) and 7 % (posterior compartment).

We found a clear statistical significant association ($p < 0.05$) between OI and POSUI for Tests 3 and 4 as well as for all test combinations (A, B and C). This association was, however, not demonstrated for Tests 1 and 2.

The odds of developing POSUI given a positive preoperative test for OI were then as follows; Test 3 OR: 6.5 (CI: 1.6-25.4), Test 4 OR: 7.1 (CI: 2.0-25.7), Test combination A OR: 9.0 (CI: 2.3-35.8), Test combination B OR: 7.7 (CI: 2.1-28.4), Test combination C OR: 6.8 (CI: 1.9-24.3).

When evaluating the test performance for predicting the outcome (POSUI) on an individual level, we tested the diagnostic accuracy of both positive and negative tests for OI. Thus, we calculated sensitivity, specificity, PPV, NPV, likelihood ratios and diagnostic ORs for all tests and test combinations. Sensitivity for the different single tests varied from 9 % to 50 %, with specificity values ranging from 88 % to 97 %. For test combinations, sensitivity ranged from 67 % to 73 %, with specificities varying from 71 % to 82 %. PPV ranged from 22 % to 50 % for single tests, with NPV varying from 83 % to 89 %. For test combinations, PPV ranged from 39 % to 44 % and NPV from 91 % to 92 %. Likelihood ratios ranged from 1.4 to 4.9 for positive single tests and 2.6 to 3.7 for positive test combinations. For negative tests, likelihood ratios varied from 0.57 to 0.97 for single tests and from 0.38 to 0.41 for test combinations. The highest diagnostic OR was seen for test combination A (DOR: 9.0 (CI: 2.3-35.8)).

Only 4.4 % (6/137) of the women developed POSUI severe enough to need treatment and only 1.5 % (2/137) underwent surgical treatment in the form of a retropubic TVT during the postoperative follow-up period.

The women participating in the POSUI study differed slightly in mean surgical age (59 vs 63 years) when compared to the total population of POP operated women during the study period, but did not differ in regards to stage of prolapse or dominating POP compartment (data not shown).

5. DISCUSSION

5.1 Methodological considerations

5.1.1 Study design and study populations

The TENT study was designed as a population-based prospective long-term observational study using current 10-year follow-up data and previously stored registry data that had been continuously recorded in the NFIR. The study did not incorporate a control group of non-operated women followed over the same time period, and some outcome data must therefore be interpreted with caution. The recurrence of stress urinary incontinence, the recurrence or occurrence of POP and urgency incontinence may be interpreted both as consequences of the surgical procedure 10 years ago as well as the effects of a normal deterioration of the pelvic floor due to advancing age. Both the prevalence of urgency incontinence symptoms (21;30-33) and POP (63) increases with age.

To ensure that women participating in the TENT study (Papers I and II) represented the “average” woman undergoing the TVT-procedure in Norway, the preoperative variables of these women were compared to the remaining women registered in the NFIR as having undergone TVT during the same time period at other hospitals not participating in the study. The preoperative variables compared are specified in section 3.1.1. The median post-void residual (PVR) was significantly lower (0 vs 5 ml, $p<0.001$), the same was the median preoperative maximum urethra closure pressure (MUCP) (40 vs 45cm H₂O, $p=0.03$) for the participating women as compared to non-participating women. The median preoperative urgency incontinence index score was significantly higher (4 vs 3, $p<0.001$) for the participating women when compared to non-participating women. However, although these are statistical differences, the clinical significance is probably negligible, as the differences

are small. If any clinical relevance should be assigned to these differences, it would be that this adds strength to the favourable outcome results for the participants, due to the fact that both a low MUCP (121) and mixed incontinence (122-124) are thought to have lower cure rates than higher MUCP and less urgency incontinence symptoms.

When including patients for the POSUI study (Paper III), we chose not to include patients with even the slightest hint of urinary incontinence, even when this was not considered relevant or in need of treatment by the patients or their doctors. This was to ensure that a preoperative positive test actually revealed occult incontinence (OI) and not only provoked a pre-existing manifest SUI. It could be argued that there is an essential difference between a positive test predicting de novo POSUI and a positive test alerting a potential worsening of an already existing SUI, even though the clinical relevance for the patients ends up being the same.

For the POSUI study (Paper III), we also wanted to test for selection bias (post study analysis). We did this by comparing study-women to other women having had POP surgery in the same time period at our Department, but who for some reason did not participate in the study. The variables compared were surgical age, preoperative stage of POP and dominating prolapse compartment. A database had been created for the POSUI study in which participants were given a study number. The identifying code-list was kept separate from the database. The participants were, however, also routinely registered in the local quality database for prolapse-operated patients at the Department. Unfortunately they were given a different number in this database. Comparing the databases in order to look for any selection bias was not planned at study start. Therefore, when the decision was made to compare study patients (study database) to other POP operated patients (controls in the local quality database), it was deemed too difficult to identify and remove study-patients from the control group as this would mean removing them

manually using two different code lists. This did weaken the comparison between the study participants and the non-study participants, as we had to use the total database of operated women as a control, which means that the study patients then also constituted 29 % of the “controls”. We do recognise that comparing study patients with a control group consisting only of POP operated patients not participating in the study would have been scientifically desirable and possibly could have generated a different result. In our analysis, however, the only difference found between the groups (of all POP operated women and the ones that were included in our study) was a slight difference in surgical age; the study patients being in mean 4 years younger at the time of surgery than the control group (59 vs 63 years). However, no differences in stage of prolapse or dominating compartment were found. The difference in surgical age was interpreted as a sign of incontinence being more frequent in older patients thereby precluding them from study participation.

The POSUI study (Paper III) was not powered to perform sub-analyses on POSUI prediction after stratifying patients based on the dominating preoperative POP compartment. The details regarding the power calculation are elaborated in section 3.6.

5.1.2 Questionnaire

The validated short-form urinary incontinence disease-specific questionnaire called NFIR questionnaire (previously named NUGG questionnaire) is used by all hospitals reporting to the NFIR (as detailed in section 3.3.1), Appendices 1 and 2 (115). It was validated as a questionnaire meant to be filled in by the patients without any help from health-professionals. However, in both the TENT study and the POSUI study, the questionnaire was used as a template for a structured interview and thereby filled in by a health professional based on the patient’s response. We do not feel that this reduces the validity of the questionnaire as this method allowed

any potential misunderstandings to be corrected immediately and thereby, in our opinion, helping to improve the quality of the patient response.

The NFIR questionnaire assesses the specific symptoms of urgency urinary incontinence and stress urinary incontinence and the severity of these symptoms by generating specified index scores (stress incontinence index score and urgency incontinence index score) as detailed under section 3.3.1. In addition, the questionnaire also generates a quality of life score (Qol index score). However, the Qol index score was not used as an outcome in the analyses for any of the papers constituting this thesis for reasons elaborated below.

The NFIR questionnaire was the only questionnaire used in this thesis for the following reasons:

1. It secured uniform comparison of the individual patient 10-year symptoms scores to the previously recorded individual symptom scores (based on the same questionnaire) in the NFIR (preoperatively and at the 6-12 months follow-up).
2. It allowed for a coherent definition of subjective urinary incontinence in all the papers.

In order to limit the number of study outcomes, we decided not to use the Qol index scores when comparing 10-year data to previously stored data. Nor did we use the Qol index to define subjective cure. We considered that the use of this derived and complex QoL score to define cure would be unsatisfactory, as a cut-off for subjective cure could vary between patients. Also, we regarded that the patients' own subjective definition of whether or not they were cured would be a simpler and possibly more reliable subjective outcome variable. We therefore created a short supplemental question to the questionnaire, enabling the patients to characterize their current leakage situation as “cured”, “better”, “unchanged” or “worse”. A total of three

supplemental questions were added to the 10-year questionnaire and used in Papers I and II, as previously described in section 3.3.1. We also had pragmatic reasons for not adding additional QoL questions or using other validated QoL questionnaires such as the IIQ-7 (125), the UDI-6 (125) or the UISS (126), which are all Grade A questionnaires recommended by the ICI (24). One important reason was the wish to keep the total questionnaire short, and thereby reduce the patients' workload, possibly increasing attendance in our 10-year follow-up study. Furthermore, using additional QoL questionnaires would require that these first were validated in Norwegian. This was deemed unnecessary, as we viewed the NFIR questionnaire supplied by the 3 new non-validated questions adequate for the studies comprising this thesis.

In regards to assessing POP symptoms, no validated questionnaire (such as the PDFI (127) recommended as Grade A by the ICI (24)) was used, as no questionnaire assessing POP symptoms was validated in Norwegian at the time of study start. At the planning stage of the POSUI study (Paper III), we discussed whether a formal translation and validation of a symptom questionnaire should be undertaken. We deemed this not to be necessary, as our study aim was not to evaluate the efficacy of POP surgery on symptom relief, but to measure the possible association between OI and POSUI and evaluate test performances of different OI tests.

The clinical investigation methods, definitions, and units in all papers constituting this thesis conform to the standards recommended by the ICS/IUGA with two exceptions. These exceptions include a different definition of recurrent urinary tract infections (UTIs) and the use of the term "occult urinary incontinence" instead of the recommended ICS/IUGA term (which is stress urinary incontinence on prolapse reduction (19)). We chose not to use the ICS/IUGA definition of recurrent urinary tract infections (UTIs), defined as at least three symptomatic and medically diagnosed UTIs during the previous 12 months (19). Instead we defined recurrent UTI in our study as

having received more than three antibiotic treatments over the last 6 months, based on the information given by the patient in the NFIR questionnaire (Appendices 1 and 2, question 8). The NFIR question regarding UTIs asks the patient how many treatments for UTIs they have received over the last 6 months categorizing into 5 category responses (“never”, “once”, “2-3 times”, “4 times” or “more than 4 times”). We defined the patients as having recurrent UTI if they chose one of the last two scores.

The reason for keeping the old term “occult incontinence” over the new ICS/IUGA term (stress urinary incontinence on prolapse reduction) when describing the stress urinary leakage that a continent woman with POP may display during provocation testing mimicking POP repair, was that we felt the new ICS/IUGA term suggests or hints of this condition being an illness or entity by its own. Occult incontinence (OI) is, in our opinion, the description of a test-result (positive). OI may also be described as a risk marker that may or may not predict a specified unwanted outcome (such as POSUI), but not by itself represent something that needs treatment.

5.1.3 Occult incontinence testing

There is to date no consensus on how best to test for OI, and no reference test has been agreed upon. As described in section 3.6, the guidelines developed by the STARD initiative were attempted adhered to when evaluating the performance of OI as a risk marker for POSUI (118). However, to fully make use of these guidelines, testing against a reference test would have been preferable when evaluating the validity of different OI tests (118). Instead, we made a selection from the wide variety of tests for OI suggested in the literature. These tests differs greatly in mode of prolapse reduction (using vaginal packing, pessary, manual/digital repositioning, forceps, speculum etc), type of provocation (Valsalva, cough, different exercise regimen or activities of daily living), positioning during testing (supine, standing, sitting, lithotomy,

semi-lithotomy) and bladder volumes during testing (83;84;86-89;92-102). From the tests suggested in the literature at the time of study planning, we therefore chose the tests detailed in section 3.3.3.

We decided against vaginal packing or the use of a speculum, as we believe these methods carries the risk of a false high number of positive tests (false positives). Using such a prolapse reduction method would imply exerting pressure on the levator ani muscles, potentially neutralizing the normal reflex contraction during coughing, with increased risk of cough related urinary incontinence. Care was taken in finding an optimally fitted therapeutic pessary ring that did not exert unwanted pressure on neither the levator ani muscles nor the urethra as an ill fitted pessary ring might obstruct the urethra resulting in a false negative for this sign (OI).

No test was performed with bladder volumes larger than 300 ml as other studies have demonstrated that no additional information is to be gained by testing beyond 300 ml (88).

The highest prevalence of OI (19 %) in our study was found when women wore an optimally fitted pessary ring over a time period of minimum 1 week. The occurrence of OI is a known side effect when using pessary as a treatment option for POP and has been shown to occur in approximately 20 % of otherwise continent POP women choosing this treatment option (128). We believe that the higher prevalence of OI found during continuous use might be explained by the fact that this allows for better testing of the patient's continence mechanisms in activities related to everyday living. The artificial office setting, in which the women are lying partly naked in the semi-lithotomic position while coughing, may have caused anxiety leading to an unintentional contraction of the pelvic floor, generating too many false negative test results.

5.1.4 Strengths and limitations

Papers I and II (TENT study)

It is generally accepted that efficacy studies of surgical treatment modalities are best investigated in randomized controlled trials. However, as this means selecting women based on strict inclusion and exclusion criteria (often treated and followed-up by dedicated doctors), an argument can be made that this might not always reflect how well a treatment performs in the general clinical setting. In Papers I and II, we instead chose to include the whole surgically treated cohort using a quality database (the NFIR) to identify the relevant study subjects. The only exclusion criterion was the inability to give informed consent. Using the national registry (NFIR), we minimized the chances of selection bias. This allowed for the study comprising all subgroups of patients offered and accepting the TVT treatment in Norway. These patients have been surgically treated by various surgeons with different levels of training and clinical performance in regards to patient numbers treated. In our opinion, this use of the total surgically treated cohort better reflected the procedure's efficacy in the “the real world” clinical setting.

The large number of patients included in the TENT study also added strengths to the external validity of the results, as it is the largest published study in the world to date evaluating long-term outcomes in women having undergone the retropubic TVT procedure.

The fact that participating Norwegian gynaecological departments (surgical units) were high-volume centres was considered an important factor conducting this type of efficacy study. Others have shown that cure rates are highly susceptible to variations in the number of patients operated within a unit per year (reflecting the volume of training each surgeon gets during a year) (129;130).

The external validity of the results in Papers I and II (the TENT study) might be questioned, as the study-population consisted of a Norwegian cohort of women living in an industrialized country with a free-of-cost public health system. The results might have looked different had the TENT study been conducted in a country where socioeconomic factors have greater impact on patient selection. However, we believe that the socio-economic situation in Norway leads to our data better reflecting the clinical needs of the whole population that undergo a TVT procedure.

Furthermore, it is important to recognize that patients registered in the NFIR are the ones selected for surgery for urinary incontinence, not reflecting the whole urinary incontinent patient population. The selection criteria used might therefore impact outcomes and the risk factors for failure might also have looked different had the whole population suffering from SUI or MUI been selected for surgery. We have no data that can compare the TVT to the non-TVT operated population, but we assume that the very young women yet to undergo pregnancies and the oldest women with severe co-morbidities and complex incontinence mechanisms may not have been offered TVT surgery as a treatment option.

Papers I and II are based on combining current data found at the 10-year follow-up with previously stored data in the NFIR. Using registry data carries the potential risk of inaccuracies in the individual entries since all information is manually and consecutively entered at the respective departments. A formal validation of variables stored in the NFIR compared to the patients' actual medical records has never been performed. However, a recent study evaluating the validity of selected data in the National Danish Urogynaecologic Database (DugaBase) found the inaccuracies of recorded data to be < 10 % for all investigated variables when compared with the individual patient's medical records (131). We can think of no conceivable reason for this to be worse for the data recorded in the NFIR, as the data is manually and consecutively

entered at the respective departments in a similar manner. We also have no reason to assume that such minor inaccuracies would have weakened the conclusions in our studies, as it is unlikely that such inaccuracies would hamper the study groups differently in a systematic manner

An additional limitation of Papers I and II is the lost to follow-up (11 %) rate. In Paper III, only 3 women were lost to follow-up. The possible impact on the results from the lost to follow-up is elaborated in section 5.1.5.

BMI at the time of surgery, as an individual risk factor for long-term failure, could not be included in the logistic regression analyses performed in Paper II, as this was not recorded in the NFIR until recently. This would have been an interesting variable to study, as previous studies have been conflicting. Several studies report good short-term outcomes for the obese women (132-134), while Hellberg et al demonstrated poorer results after a mean follow-up of 5.7 years for women with BMI > 35 (135). However, we did record the BMI at the 10-year follow-up in our TENT study. If the lowest BMI class is ignored (and this class included very few patients), there seem to be a significant increase in subjective failure with increasing BMI. Notably, this is the BMI at the 10-year follow-up and not at the time of surgery. The results of these analyses are presented in table I below, and not published in any of the papers. For objective failure, no such association could be found. Using the same cut-off for surgical age as in the logistic regression analyses (≤ 56 years), the same trend of a higher subjective failure rate in women with higher BMI was observed in both age categories, but this was not found for the objective failure rates (data not shown). Both symptoms of SUI and UII are known to increase with increasing BMIs (136). The discrepancy between subjective and objective failure rates could possibly be the result of differences in sample size. There were considerably less women with available BMI information that had been submitted to a stress test at the 10-year follow-up compared to the number of women filling in the questionnaire.

Table I

10-year failure rates for the whole cohort according to BMI at the 10 year follow-up

BMI (kg/m²) at the 10-year TENT follow-up	10-year incidence of objective failure n = 316 (11 missing)	Fisher's Exact Test P value	10-year incidence of subjective failure n = 481 (2 missing)	Fisher's Exact Test P value
< 18.5 (underweight)	50.0 % (n = 2) not included in the risk analysis	0.831	25.0 % (n = 4) not included in the risk analysis	0.046
18.5-24.9 (normal weight)	9.0 %		22.3 %	
25.0-29.9 (overweight)	11.3 %		23.8 %	
> 30 (obese)	9.2 %		35.4 %	

Although the 10-year TENT follow-up BMI could be regarded as a proxy for BMI at the time of surgery, it remains an uncertain variable. Many patients loose weight after having undergone incontinence surgery, allowing them to resume an active physical lifestyle, thereby changing BMI category

postoperatively. In addition, many women put on weight when getting older (137). The BMIs at the 10-year follow-up were thus not included in the logistic analyses of risk factors for failure after TVT in Paper II.

Paper III (POSUI study)

To our knowledge, the POSUI study (Paper III) is one of only a few studies that, with an adequate sample size, have been able to demonstrate the statistical association between OI and POSUI. This association was also demonstrated in the non-intervention arm of the CARE trial (88). The POSUI study is also one of the first non-intervention studies published and thereby contributes important non-biased knowledge of POSUI incidences after POP surgery (89;98;104;105;138). Later there have been additional non-intervention studies published (101;111;139). With the exception of testing against a reference test, we adhered to the guidelines for evaluating and reporting recommended by the Standard for Reporting of Diagnostic Accuracy (STARD) initiative (118). This implies a full evaluation of the diagnostic accuracy, not just the sensitivity and specificity but also PPV, NPV, LR+, LR- and the DORs.

In this paper, it might be argued that the time from surgery to the follow-up visit might be too short in order to identify all patients developing bothersome POSUI warranting incontinence surgery. The mean postoperative follow-up was 5 months. Some women might in theory be unwilling to undergo new surgery so soon after their POP surgery, although we have no actual knowledge of this being true for any woman participating in the study. In the non-intervention arm of the CARE trial, the percentage of women meeting the stress incontinence endpoint was approximately the same at two years compared to the 3-months postoperative assessment (140). We therefore conclude that a longer follow-up time than 6 months would not likely have significantly impacted our conclusions.

It might also be argued that the heterogeneity regarding the types of pelvic organ prolapses included in the POSUI study and types of prolapse surgeries performed may have had a significant impact on the result. However, the heterogeneity was deliberate, as we wanted to identify an occult incontinence (OI) test (or a test combination) simple enough to be implemented in an ordinary clinical setting comprising a heterogeneous POP population. OI can be demonstrated by prolapse reduction in any compartment, even when there is only an isolated defect in the posterior vaginal wall (141). Performing a subgroup analysis on the women having undergone the Manchester procedure (67 % of our total POSUI study population), we found no difference in test performance regarding the prediction of POSUI when compared to the total study population (data not shown).

No synthetic vaginal meshes were used in the POP repairs of the women included in this study. This was due to the fact that our Department has been sceptical of using synthetic meshes in vaginal POP surgery. The potentially severe complications in some patients (such as mesh exposure) leading to the FDA warning of restricted use in vaginal surgical repairs, has given further support to our policy of preferring the native tissue repair methods for POP surgeries. Our Department has had a quality database in which subjective and objective 1-year postoperative results have been consecutively stored since 2002. This has shown such good subjective and objective results after native tissue repair that a transition to mesh surgery was never deemed necessary (142). Synthetic meshes used in the anterior compartment have also been associated with a higher rate of POSUI than traditional surgery using native tissues, possibly due to overcorrection of the anatomy (106;107).

We recognise that excluding patients with minor symptoms of incontinence from participating in the POSUI study (see flowchart of Figure I, Paper III), even if this gave no bothersome symptoms, may have reduced the clinical relevance of the study as many POP patients have a minor degree of

SUI. Such a patient selection could also have contributed to the low percentage of clinically significant POSUI shown in our study. However, as previously detailed above in section 5.1.1, we believe there is a principal difference between a positive provocation test revealing OI in an otherwise continent woman and a test causing aggravation of already existing SUI symptoms (even minor). Only the former can in our opinion be called “true” OI.

No blinding of the surgeons or the doctors performing the postoperative evaluations in regards to the preoperative test results was done in the POSUI study. However, we do not believe this had any significant impact on the outcomes and conclusion in our study due to the fact that type of surgery was decided upon before testing, and our primary outcome was based on subjective information supplied by the patients on a validated questionnaire. The patients themselves were not actively informed about their preoperative testing status.

5.1.5 Statistical analyses

Missing values/Lost to follow-up

The calculated results in both the TENT study (Papers I and II) and the POSUI study (Paper III) were based on per protocol analysis. An alternative approach could have been to use Intention to treat (ITT) analysis applying the Last-Observation-Carried Forward (LOCF) approach when analyzing the outcomes in Paper I, as this was an efficacy study evaluating a treatment modality. However, we discarded the Last-Observation-Carried Forward (LOCF) method for the following reason: Our study population was originally not selected as participants in a clinical trial at the treatment decision time (10-12 years ago). The data from the TVT operated women were only sent (de-identified) to the NFIR at the time of surgery and at the 6-12 months follow-up as a quality assurance measure for the treatment given. When it was decided to use these data in the TENT study (Papers I and II) and merge them with the

10-year follow-up data, additional written consent had to be obtained from the women participating in the study. This written consent was given by the women at the 10-year follow-up visit, and consent to use previously stored data from women not participating could therefore not be obtained. This precluded the use of LOCF in Paper I.

The number of women lost to follow-up comprises a challenge to any study, including ours. When conducting a long-term follow-up study 10 years after the initial treatment the challenge is multiplied, as even some women satisfied with the treatment may not find time in their busy life allowing them to visit the clinic. Furthermore, it is conceivable that some women might be so disappointed with their treatment or have no confidence left in those working at their local hospitals, resulting in them not wanting to participate in a follow-up study. A high lost to follow-up will inevitably impact the statistical power of the study. Furthermore, it may generate bias, and thereby reduce the confidence in the results. We tried to minimize the lost to follow-up rate by offering women, who declined coming to the outpatient clinic, a structured telephone interview for subjective data. In the TENT study (Papers I and II), lost to follow-up was only 11 %, after excluding women who were no longer alive at the time of follow-up. We made no assumption whether these lost to follow-up women, or deceased women, were most likely to be categorized as TVT cures or failures. All analyses were done as per protocol analysis, as detailed above. However, we do not find it likely that women declining participation were less satisfied with the treatment than those participating. We believe the opportunity for a clinical evaluation is a strong incentive for patients with failed surgery or for those dissatisfied with their treatment to participate.

We would have appreciated a possibility to evaluate potential bias by comparing participating women with those declining participation on baseline characteristics. However, as previously detailed, the written consent for

accessing previously stored data in the NFIR and the medical records were first given at the 10-year follow-up visit, precluding this possibility. All women having their data stored in the NFIR had, however, originally signed a consent form allowing the NFIR to use de-identified data in statistical analyzes comparing hospitals. We were therefore able to compare stored data of participating women to women operated at other hospitals in the same time period (as described in section 3.1.1). No clinically relevant differences were found. The authorized personnel at the NFIR performed these comparative analyses, and the results are presented in Paper I. We therefore assume that the women who were lost to follow-up most probably would distribute themselves equally in all outcome groups. Notably, this assumption is not supported by strong data, and thus possible bias caused by selection should be taken into account when interpreting the results.

Logistic regression model/Receiver-operating characteristics (ROC)

In Paper II (the TENT study), a multivariate logistic regression model was built to test potential risk factors (variables) against two separate outcomes. All the independent variables tested in the model generated in Paper II were also tested for possible effect modifications (interactions), but none were found. The model was also tested and found sound with a goodness-of-fit test (Hosmer-Lemeshow) when the variable for surgical age had been dichotomized using receiver-operating characteristics (ROC). By using ROC, the “ideal” cut-off value providing both the highest sensitivity and the highest specificity for the outcome can be identified. This is easily located on a ROC curve by finding the point highest on the vertical axis and the furthest to the left on the horizontal axis (upper left corner). The same surgical age (56 years) turned out as cut-off for both outcomes. Thus surgical age could then be dichotomized using 56 years as cut-off when both outcomes were analysed in the multivariate models.

5.2 Discussion of results

Paper I

Paper I reports on the long-term efficacy of the tension-free vaginal tape (TVT) procedure. We found an objective cure rate of 89.9 % after 10 years for the whole heterogeneous patient cohort. When we compared the objective cure rate to the 6-12 months follow-up data there was no statistical difference ($p = 0.86$). Others have also reported objective cure rates ranging from 84 % to 93.1 %, but their long-term follow-up studies have been on smaller and more selective study populations (143-146). There is, to our knowledge, only one other study that has shown equally sustainable objective results over a 10-year period (145). This study from Serati et al also found sustainable subjective results over the same 10-year period (145). In our study, however, there was a small but significant decline in women stating “very satisfied” with their treatment from the 6-12 months follow-up visit to the 10-year follow-up visit ($p = 0.006$). The subjective cure rate demonstrated in our study (76.1 %) is also within the 65 % - 89.7 % range found by others (143-147). We argue that both the difference in objective and subjective cure rates (89.9 % vs 76.1 %) and the decline in women stating “very satisfied” over the 10-year follow-up period can be explained by the development of de novo urgency incontinence symptoms. This assumption is based on the fact that we were able to demonstrate a much lower median urgency incontinence index score in the group of women stating either “cured” or “very satisfied” when compared with the others (0 vs 4.5, $p < 0.001$ and 0 vs 5, $p < 0.001$ respectively). When specifically evaluating the rate of women stating “very satisfied” with their surgical treatment 10-year post surgery, we have concluded that 82.6 % “very satisfied” women is a satisfactory result given our heterogeneous patient population. This result is also well above the 74 % satisfaction rate demonstrated in a comparable study population from Sweden (144). More

women in our study considered themselves satisfied with the treatment than cured. This fact that some women are satisfied even if not completely cured resonates well with a publication from Oh et al, which reported that the frequency of incontinence episodes and the volume of leakage are the most dominating symptoms related to self-perceived disease (148). Therefore if these symptoms improve, the subjective satisfaction rate will likely improve, even if other symptoms are still present. Even though we did not specifically investigate whether these same variables were closest linked to patient satisfaction in our study, we believe this to be the most probable explanation for the difference between subjective cure rate (76.1 %) and satisfaction rate (82.6 %) found in our study.

The subjective cure rate of 76.1 % demonstrated in our long-term follow-up TENT study is also far better than the 44 % demonstrated 14 years after Burch colposuspension, which used to be the previous gold standard in SUI surgery (47).

The SUI re-operation rate (2.3 %) found in Paper I is in accordance with the 1.7 % - 5.6 % demonstrated in most long-term follow-up studies (146;147;149). In a study from Jonsson Funk et al, a cumulative incidence of 13 % for new SUI surgery was found (150). However, these authors did not study retropubic TVT in particular, but compiled all types of slings and calculated cumulative incidences. It is therefore difficult to make a direct comparison between their re-operation rates and the re-operation rates found in our study.

Our study revealed a 4.2 % incidence of subsequent POP surgery (during the 10-year follow-up) seemingly contrasting other studies, in which very low rates of POP after TVT has been found (151;152). It has, in the past, been thought to be an association between the development of POP and having undergone an incontinence procedure at the bladder neck (such as the Burch procedure) (153;154). This association has, however, not been demonstrated

after TVT (151;152). Even though we did find a higher incidence of POP after TVT than what has been demonstrated by these other studies, our study was not designed to systematically evaluate persistence or de novo POP development after TVT, beyond recording any subsequent POP surgery. The incidence of 4.2 % should therefore not be interpreted as the true post-TVT incidence of POP.

We identified a post void residual (PVR) above 100 ml in 3.5 % of the women at the 10-year follow-up visit, which was a significant increase both from the 0.3 % identified before surgery and the 0.7 % found at the 6-12 months follow-up visit. However, an overestimation of PVR might have occurred as the PVRs were only measured once, and repeat measurements have been shown to identify lower volumes (155).

As detailed in section 5.1.1, we found it difficult to ascribe what impact the surgery done 10-years earlier posed, and what impact the normal deterioration of the pelvic floor due to ageing had on the recurrence of SUI or the occurrence of POP and urgency incontinence 10 years after TVT surgery. However, comparing the preoperative data of PVRs with the 6-12 months and 10-year follow-up data, we found that the greatest increase in number of women with PVRs > 100 ml occurred in the time period between the 6-12 months follow-up and the 10-year follow-up. This probably indicates that the ageing component is the most important determinant for long-term voiding dysfunction, not the incontinence surgery per se. The same was noted for de novo urgency incontinence rates at 6-12 months and 10-year follow-up when only looking at women with no preoperative urgency incontinence symptoms, again indicating increasing age as the most probable determinant.

A clinical worrisome high rate (22.8 %) of women stating subjective voiding difficulties was found at the 10-year follow-up. This was calculated from a supplemental question added to the 10-year questionnaire and could therefore not be compared with previous data. Nevertheless, it may be

speculated that this also represents a normal ageing effect on the lower urinary tract. Of the 22.8 % that stated subjective voiding difficulties, the majority complained of a slow or intermittent urinary stream. We were not able to correlate this to any objective measures of voiding dysfunction such as high PVRs or low Q_{\max} . In fact we found no differences in low Q_{\max} (defined as $Q_{\max} < 15$ ml/s) between women stating voiding difficulties and the others (27.7 % vs 27.1 %, $p=0.92$). Nor did we find any significant differences in the percentage of women stating that they were “very satisfied” with their treatment when women stating voiding difficulties were compared to women stating no such difficulties (83.2% vs 82.3%, $p=0.84$). This has led us to the conclusion that the reported voiding difficulties do not represent a serious clinical problem for these women at the present time. However, since no voiding cystometry was performed, we cannot exclude a partial obstruction developing over time with compensatory increased detrusor pressures coexisting with normal urinary flows and an absence of high PVRs. Nor can we, without a control group of none-operated age-matched women, rule out the possibility that having a synthetic sling implanted speeds up or worsens the tissue deteriorating effects associated with an ageing pelvic floor. Further ageing could therefore theoretically cause these patients to experience increasing voiding difficulties in the future.

The NFIR questionnaire lack information on urgency symptoms without incontinence (named overactive bladder dry: OAB dry), as it was created as an incontinence-specific questionnaire. When used post surgery it can, however, provide information on urgency incontinence symptoms (named overactive bladder wet: OAB wet). As we wanted to calculate the long-term de novo urgency incontinence rates, we looked at the sub-cohort of women with pure SUI symptoms without any preoperative symptoms of urgency incontinence (preoperative urgency incontinence index score = 0) operated with the TVT procedure (21 %). When any new urgency incontinence symptoms resulting in

an urgency incontinence index score > 0 (at the 10-year follow-up) was used as a definition of de novo urgency incontinence, a de novo urgency incontinence rate of 41.6 % was found (data not published). However, many of the women stating some urgency incontinence symptoms did not report any need for pad use (one of the Qol questions in the NFIR questionnaire). We therefore decided to redefine de novo urgency incontinence with inclusion of the need for pad use. The definition decided upon therefore read: The development of postoperative urgency incontinence symptoms (urgency incontinence index score > 0) combined with the need for pad use among women with no preoperative symptoms of urgency incontinence (preoperative urgency incontinence index score = 0). Thus the rate of de novo urgency incontinence was, by this definition used in our study, found to be 14.9 % and in accordance with the 1-17 % reported by others (147;152;156).

Paper II

Paper II reports on preoperative and operative risk factors for long-term failure. Although the TENT study showed high cure rates for the whole non-selected heterogeneous cohort, there were differences in failure rates (absolute risks) when participating women were subdivided by their individual preoperative and operative characteristics.

We believe it to be essential for women contemplating surgery to receive as comprehensive information as possible regarding the likelihood of long-term success, as this may vary from woman to woman based on their individual characteristics. In this paper, we therefore created a multivariate logistic regression model in which we tested different potential preoperative and operative risk factors for long-term failure. The same model was used to test the potential risk factors against both long-term subjective and long-term objective failure (for definitions see section 3.5.1).

A high surgical age emerged as a risk factor for both outcomes. We are unaware of any other study having demonstrated this association between high surgical age and a poor long-term (10-year) objective outcome. There is, however, one publication reporting an association between increasing age (by decade) and objective failure at 2 months follow-up (157). Regarding the association between high age and long-term subjective failure, this was previously reported by Hellberg et al (135). In their study, a poorer outcome was found among those over the age of 75 (at the time of follow-up) after a mean follow-up time of 5.7 years. However, in contrast to them only finding an increased failure rate among the very old, we demonstrated a clear difference in outcome at a much younger age (56 years at the time of surgery) using receiver-operating characteristics (ROC). The rationale for using ROC is fully explained under section 5.1.5. The cut-off at a surgical age of 56 years is close to the 51 years found to be the median age of spontaneous menopause (158). We have therefore speculated that our finding might be related to a weaker support of the pelvic floor at the time of surgery in the oldest age group. A weaker pelvic floor support might be caused by the age-induced loss of muscle strength and/or the impairment of the elastic quality of connective tissue that are known to accelerate after menopause (159;160).

Experiencing surgical complications at or immediately following surgery was also found to be a risk factor for long-term subjective failure. This has to our knowledge also not been demonstrated previously. The low numbers of complications prevented analysis regarding specific types of complications and the complications were therefore in the model dichotomized into yes or no. A conceivable explanation regarding how surgical complications can be a risk factor for failure would be that this in some way is linked to the development of urgency and urgency incontinence. We know that the urethra is an organ possessing complex neuromuscular reflex pathways that modulate bladder function (161). It is possible that any excess damage to these delicate

structures could lead to excess collagen deposition and scarring that in turn would lead to urgency or urgency incontinence. Such excess damage could be caused by repeated needle placement after bladder perforation, haematomas, infections or re-intervention for sling release. There is strong indication, in the literature, that urgency is an independent risk factor for reduced patient satisfaction after TVT surgery (162;163). In support of this concept, we demonstrated in Paper I that the median urgency incontinence index 10 years after surgery was higher among women **not** claiming to be cured or **not** stating “very satisfied” with the treatment given when compared to the others (detailed above under Paper I).

The fact that complications are associated with increased long-term failure rates also underscores the importance of this type of surgery being performed by (or under guidance of) skilled surgeons only. This is also emphasized by others demonstrating an inversely association between failure rates and the number of TVT procedures performed by each surgeon (129;130).

Our study confirms that women with preoperative diagnosed MUI treated with retropubic TVT have a poorer long-term subjective outcome than women with pure SUI, a finding that has also been reported by others (122-124). However, we were also able to demonstrate that the urgency incontinence symptoms (measured by the stored preoperative urgency incontinence index score) need to be of a certain magnitude for it to have an impact on the outcome. MUI patients with only a small or moderate component of urgency incontinence symptoms (urgency incontinence index < 5) did not significantly differ from pure SUI patients in regards to failure rates. The significance of the urgency incontinence component in MUI women on surgical results after TVT has also been verified in a study from Kulseng-Hanssen et al from 2008 (52).

Interestingly, neither the degree of preoperative stress incontinence symptoms, as expressed by preoperative stress incontinence index scores, or the amount of preoperative stress leakage on pad stress testing was found to be risk factors for long-term failure. This fact is also reported by others (162;163). However, in a prospective cohort study from Cammu et al, the use of more than 2 diapers a day was associated with failure after TVT in a multivariate logistic regression analysis (157). However, in their study the diapers were worn throughout the day and would therefore, in our opinion, likely comprise both stress and urgency incontinence episodes making it significantly different from the cough/jump pad stress test used in our study. This is also supported by the fact that they did not demonstrate the same association with failure rates when performing a cough stress test in the sitting position with 300 ml bladder volume.

Furthermore, we were not able to detect any negative impact on the outcome from previous SUI surgery, concomitant POP surgery or low preoperative MUCPs in our study. The literature is here more conflicted. Rardin et al (164) found no difference in cure rates among women undergoing primary or repeat SUI surgery contrasting later publications from others demonstrating increased odds for failure when repeat midurethral sling procedures are performed (157;165). Low preoperative MUCPs (< 20 cm H₂O) not being a risk factor for failure after retropubic TVT has also been demonstrated by others (54;124;130). However, in a study from Clemons et al, a MUCP \leq 15 cm H₂O was associated with short-term TVT failure (121).

Concomitant POP surgery did not seem to increase the risk of failure for patients with both manifest SUI/MUI and POP. There is conflicting evidence in the literature as similar results have been found by some authors (157;162;163) while others such as Pang et al have demonstrated concomitant POP surgery being associated with inferior results (166). These differences

might be explained by population differences resulting from which patients are selected for concomitant procedures.

Paper III

This paper verifies the existence of an increased risk for postoperative stress urinary incontinence (POSUI) after POP surgery in preoperatively continent POP patients demonstrating occult incontinence (OI). This association was found for provocation Tests 3, 4 and all test combinations, but not for Tests 1 and 2, probably due to a sample size problem (lowest prevalence of OI in Tests 1 and 2). The tests are detailed in 3.3.3. The POSUI study (Paper III) is one of a very few non-intervention studies with sufficient sample size to demonstrate the existence of this often assumed association, another being the Colpopexy and Urinary Reduction Efforts (CARE) trial (88).

However, the existence of an association between OI and POSUI on a population level cannot alone be used as an argument for recommending prophylactic anti-incontinence surgery at the time of POP surgery on an individual level. The main additional consideration is that adding an anti-incontinence procedure may carry a potential risk to the patient including longer operating time, voiding dysfunction due to bladder outlet obstruction, de novo OAB symptoms, vaginal mucosa extrusions and increased costs. The risk of intervention following bladder outlet obstruction was in a publication from Ballert et al found to be 9.7 % (108). In order to properly decide whether a woman with OI should be offered a prophylactic anti-incontinence procedure, it is therefore essential to know the validity of the tests by which OI has been diagnosed. The validity describes the tests performance in predicting the outcome by means of sensitivity, specificity, PPV, NPV, the likelihood ratios for positive (LR+) and negative (LR-) test results and diagnostic odds ratios (DORs).

We chose to follow the Standard for Reporting of Diagnostic Accuracy (STARD) initiative from 2003 when evaluating and reporting the test results for OI, with the exception of using a reference test (118). The reason is that there is to date no consensus on a reference test for OI. Despite having demonstrated a clear statistical significant association between OI and POSUI, all our proposed tests and test combinations showed equally poor performance predicting on the individual level. This illustrates that ORs may not be the appropriate tool for describing the ability of a risk marker (such as OI) to identify patients likely to end up with a disadvantageous outcome (such as POSUI). ORs and relative risks (RRs) are epidemiological instruments frequently used to assess associations, but are argued by some to be poor instruments when using risk markers to predict outcome for individuals (167).

The incidence of POSUI in our study was 17 % when defined as subjective incontinence (validated questionnaire). This result is in the lower end of the 11 % - 44 % range demonstrated by others (89;101;104;105;138). Stratified by dominating preoperative compartment (anterior-, mid- and posterior), the POSUI incidences were 20 %, 18 % and 7 % respectively. The low incidence might have been affected by the rigid exclusion of anyone with a hint of pre-existing urinary incontinence, as detailed in section 5.1.4. It could also be ascribed to the fact that the prolapse repair itself might function as an anti-incontinence procedure. Borstad et al performed a randomized trial, published in 2010, in which women with POP and SUI were randomized to either TVT at the time of POP repair or three months later (168). They found a 29 % cure rate of SUI and no need for subsequent TVT in the group of women having had prolapse repair alone, even without any specific dissection under urethra or Kelly placements during the POP surgery (168).

A few patients in our study were found to have objective evidence of leakage in the postoperative evaluation without having any symptoms. The clinical significance of this finding in asymptomatic patients is yet to be

established. It is possible that these women have an increased risk of developing SUI later in life.

The prevalence of OI found with the tests evaluated in the POSUI study was lower (4 %-19 %) than previously demonstrated by others (83;84;93-96;99). We contribute this to several reasons. One obvious reason being that different methods of testing are often used due to the lack of standardization, as detailed in section 5.1.3. In addition there may be clinical differences between the cohorts tested, as some studies have included patients who have responded “rarely” when asked about stress urinary incontinence on a validated questionnaire. We would argue that these women (answering “rarely” rather than “never”) already have a small (although insignificant) manifest SUI and are likely to more often have a positive provocation test than those denying any degree of SUI on all questions.

The POSUI study revealed further that POP patients not demonstrating OI are still at risk of de novo POSUI. We found a 9 % incidence of POSUI among women negative on all four preoperative tests for OI. Again the literature is conflicting. Some recent studies have published similar results to ours (88;89;101;108), while several older studies report only a slight risk of POSUI or none at all in patients without OI (96;97;113;169). Furthermore, there are large studies reporting that POSUI may also occur after performing concomitant prophylactic anti-incontinence procedures (101;105).

Only six patients (4.4 %) in our observational study developed symptomatic POSUI severe enough to warrant treatment. Only two of those patients (1.5 %) needed an anti-incontinence procedure (TVT) some time after their POP surgery. The remaining four women were treated with pelvic floor muscle training. This is even lower than the 7.7 % - 8.3 % of POP operated continent women needing subsequent SUI surgery for POSUI demonstrated by others (108;170). Looking specifically at the subgroup of occult incontinent women having POP surgery without anti-incontinence procedures, Ennemoser

et al recently published 2-8 years follow-up data (111). In this population only 5.3 % of the women had received a subsequent TVT procedure for POSUI. A higher percentage (15.8 %) was found by Jundt et al (170). Furthermore, the number needed to treat with prophylactic TVT in order to prevent one preoperatively continent woman from having a subsequent TVT after POP surgery has been estimated in two randomized controlled trial to lie between 6 and 11 (101;139).

The low percentage of POSUI found in our study, combined with the estimate of up to 11 women having to receive an “unnecessary” procedure with potential life-long implications on voiding function to prevent one subsequent incontinence procedure found by others, has led us to the conclusion that the current “two-step” approach within our Department seem the most viable approach for the future.

A further argument for the “two-step” approach is the long life expectancy of women and the unknown effect of a TVT after several decades. Many women in Norway may now expect to live until 100 years of age, and many of these might be in need of an incontinence procedure decades after a POP operation. To day, no studies have looked at the life-long effects of performing unnecessary TVT at younger age, concomitant with the POP repair (the “one-step” approach) and whether this reduces the beneficial effect of a new incontinence procedure performed at older age.

6. CONCLUSIONS

This thesis demonstrates that the retropubic tension-free vaginal tape (TVT) procedure has a very satisfactory long-term subjective and objective outcome with a low re-operation rate. The procedure has good efficacy, even when used on an unselected heterogeneous cohort of women with numerous surgeons in a high-volume clinical setting across different hospitals.

Our TENT study showed a small decline in treatment satisfaction seen over the 10-year follow-up period despite no change in objectively measured results. We believe this is explained by the increase in urgency incontinence symptoms seen during the follow-up period. The relationship between increased urgency incontinence symptoms and reduced patient satisfaction is demonstrated by the fact that women **not** stating “very satisfied” with the treatment had significantly more urgency incontinence symptoms at the 10-year follow-up visit (higher urgency incontinence index scores) compared to the women reporting to be “very satisfied” with the treatment.

The TVT procedure had few serious surgical complications registered at or immediately following surgery, but the total surgical complication rate was almost one in ten (8.7 %). Experiencing a surgical complication also seems to be an individual risk factor for long-term failure and underscores the importance of this surgery being performed by (or under the guidance of) experienced surgeons. Among the long-term unfavourable outcomes registered, de novo urgency incontinence and subjective voiding difficulties were the most prominent reported by the women. The most frequently stated voiding difficulty was the feeling of a slow or intermittent urinary stream. However, no significant difference in percentage of women declaring themselves “very satisfied” with the operation was found comparing women stating voiding difficulties to women stating no such difficulties. Furthermore,

few women were found to have objectively measurable voiding difficulties at the 10-year follow-up (low Q_{\max} and/or high PVRs).

Whether the reported de novo urgency incontinence or the subjective voiding difficulties are related to the procedure given 10 years ago, or are related to normal deterioration of the pelvic floor caused by advancing age, cannot fully be answered by this thesis.

We found the long-term (10-year) failure rate after retropubic TVT to be low for the whole cohort studied. However, a surgical age ≥ 56 years, high degree of preoperative urgency incontinence symptoms and surgical complications all seem to exert a negative impact on the long-term outcome. The negative effect of mixed urinary incontinence (MUI) was only seen when the amount of urgency incontinence symptoms was severe. Thus having MUI is not by itself a risk factor for failure. MUI women, in whom the component of urgency incontinence symptoms was below 5 on the urgency incontinence index, did not display any increased risk of long-term failure when compared to women having a pure SUI. Neither the degree of stress incontinence symptoms, amount of stress urinary leakage, previous SUI surgery, low preoperative MUCP or concomitant POP surgery were found to assert any negative impact on the long-term outcome.

This thesis demonstrates further (with the POSUI study) that very few preoperatively continent women develop POSUI severe enough to warrant later incontinence surgery after POP surgery. There is a positive statistical association between occult incontinence (OI) and the risk of developing POSUI after POP surgery on a population level. However, even though this association is seemingly strong (high ORs), OI is a poor risk marker for identifying individual women in need of prophylactic anti-incontinence surgery at the time of POP surgery.

7. RECOMMENDATIONS AND CLINICAL PERSPECTIVES

The findings in this thesis should be presented to women contemplating incontinence surgery or pelvic organ prolapse repair. The fact that retropubic TVT has far better long-term results than any previously used surgical method for SUI and MUI makes TVT the method of choice offered to women when surgical treatment for these conditions is considered. At present, we do not know whether the new modified mid-urethral slings can demonstrate similarly excellent long-term results. As this type of surgery is not for a life threatening disease, the women should be informed that the operation is irreversible and that their voiding function might be affected. They should be made aware that, even though few women develop objectively measurable voiding impairment, almost one in four state subjective voiding difficulties and 15 % develop new urgency incontinence symptoms during the first 10 years after surgery. Both conditions are difficult to treat and might impair quality of life. However, the information should be balanced, as one cannot with absolutely certainty contribute these lower urinary tract symptoms to the procedure itself, as it might just as well be related to a normal age related deterioration of the pelvic floor.

By taking the women's individual preoperative characteristics into account, a more accurate and realistic information regarding long-term results from retropubic TVT surgery can be given prior to the operation. Women with individual risk factors for failure might in this way be forewarned that a good short-term result might not be lasting a lifetime and that there might be a need for additional treatment later in life.

The findings of this thesis will help empowering both women and physicians to better decide whether or not to opt for surgery as a treatment option for a condition that is not life threatening but severely reduces the quality of life for a great number of women.

Concomitant POP surgery does not seem to negatively impact the long-term outcomes of TVT surgery in women with concomitant urinary incontinence and POP, in favour of a “one-step” approach. However, there is a great difference in offering a “one-step” approach to women suffering from both incontinence and POP and offering it as a prophylactic procedure to POP women with no symptoms of SUI or MUI. When investigating preoperatively continent women undergoing POP surgery, we found a very low number of patients in need of additional incontinence surgery after POP surgery. Therefore, offering TVT as a prophylactic anti-incontinence procedure to every continent woman undergoing POP surgery hardly seems ethical and not clinically justified. Even though we were able to demonstrate an association between OI and a risk for POSUI on a population level, the predictive value of OI as a marker for identifying individual women at risk for POSUI was so poor that it cannot be considered ethically justified to offer TVT as a prophylactic procedure even to these women.

As a consequence, there seems to be no benefit in occult incontinence testing prior to POP operations. This time-consuming preoperative evaluation should therefore be omitted from the preoperative evaluation of continent women planning POP surgery, as it has no demonstrable benefit or clinical relevance. Furthermore, continent women demonstrating leakage on barrier tests (such as a pessary) should not be told that they have an increased risk of developing POSUI, they should rather be reassured that the risk is low, and that there is additional help in the form of a procedure with excellent long-term results to be given should they be among the few developing POSUI (in a “two-step” setting).

The recommendation of this thesis is to reserve incontinence surgery in POP patients for the few patients who develop bothersome POSUI after the POP surgery (using a “two-step” surgical approach).

8. ERRATA

Paper II: Table I: the upper tertile for the preoperative stress tests in the first column of the table should read > 66.7 percentile, **not** > 66.1 percentile.

Paper III: Last page, first paragraph in the discussion section should read: Our selected group did, however, differ slightly in age, being on average 4 years younger than the total group. **Not 3 years** as it currently reads in Paper III (59 vs 63 years).

9. OTHER PUBLICATIONS DURING THE PHD PERIOD

Oversand SH, Staff AC, Spydslaug AE, Svenningsen R, Borstad E.

Long-term follow-up after native tissue repair for pelvic organ prolapse

Int Urogynecol J. 2013 Jul 6 [Epub ahead of print]

10. REFERENCE LIST

- (1) Kearney R, Sawhney R, Delancey JO. Levator ani muscle anatomy evaluated by origin-insertion pairs. Obstet Gynecol 2004;104:168-73.**
- (2) Delancey JO. Anatomic aspects of vaginal eversion after hysterectomy. Am J Obstet Gynecol 1992;166:1717-24.**
- (3) Tansatit T, Apinuntrum P, Phetudom T, Phanchart P. New insights into the pelvic organ support framework. Eur J Obstet Gynecol Reprod Biol 2013;166:221-5.**
- (4) Badiou W, Granier G, Bousquet PJ, Monrozies X, Mares P, de TR. Comparative histological analysis of anterior vaginal wall in women with pelvic organ prolapse or control subjects. A pilot study. Int Urogynecol J Pelvic Floor Dysfunct 2008;19:723-9.**
- (5) Boreham MK, Wai CY, Miller RT, Schaffer JI, Word RA. Morphometric analysis of smooth muscle in the anterior vaginal wall of women with pelvic organ prolapse. Am J Obstet Gynecol 2002;187:56-63.**
- (6) Rud T, Andersson KE, Asmussen M, Hunting A, Ulmsten U. Factors maintaining the intraurethral pressure in women. Invest Urol 1980;17:343-7.**
- (7) Berkow SG. The corpus spongiosum of the urethra: its possible role in urinary control and stress incontinence in women. Am J Obstet Gynecol 1953;65:346-51.**
- (8) Delancey JO, Morgan DM, Fenner DE, Kearney R, Guire K, Miller JM, et al. Comparison of levator ani muscle defects and function in women with and without pelvic organ prolapse. Obstet Gynecol 2007;109:295-302.**
- (9) Delancey JO, Kearney R, Chou Q, Speights S, Binno S. The appearance of levator ani muscle abnormalities in magnetic resonance images after vaginal delivery. Obstet Gynecol 2003;101:46-53.**
- (10) Goepel C. Differential elastin and tenascin immunolabeling in the uterosacral ligaments in postmenopausal women with and without pelvic organ prolapse. Acta Histochem 2008;110:204-9.**

- (11) **Ewies AA, Al-Azzawi F, Thompson J. Changes in extracellular matrix proteins in the cardinal ligaments of post-menopausal women with or without prolapse: a computerized immunohistomorphometric analysis. Hum Reprod 2003;18:2189-95.**
- (12) **Moalli PA, Shand SH, Zyczynski HM, Gordy SC, Meyn LA. Remodeling of vaginal connective tissue in patients with prolapse. Obstet Gynecol 2005;106:953-63.**
- (13) **Altman D, Granath F, Cnattingius S, Falconer C. Hysterectomy and risk of stress-urinary-incontinence surgery: nationwide cohort study. Lancet 2007;370:1494-9.**
- (14) **Forsgren C, Lundholm C, Johansson AL, Cnattingius S, Zetterstrom J, Altman D. Vaginal hysterectomy and risk of pelvic organ prolapse and stress urinary incontinence surgery. Int Urogynecol J 2012;23:43-8.**
- (15) **Jelovsek JE, Barber MD. Women seeking treatment for advanced pelvic organ prolapse have decreased body image and quality of life. Am J Obstet Gynecol 2006;194:1455-61.**
- (16) **Tennstedt SL, Fitzgerald MP, Nager CW, Xu Y, Zimmern P, Kraus S, et al. Quality of life in women with stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2007;18:543-9.**
- (17) **Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol 1997;89:501-6.**
- (18) **Fialkow MF, Newton KM, Lentz GM, Weiss NS. Lifetime risk of surgical management for pelvic organ prolapse or urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2008;19:437-40.**
- (19) **Haylen BT, de RD, Freeman RM, Swift SE, Berghmans B, Lee J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Int Urogynecol J 2010;21:5-26.**
- (20) **Mannella P, Palla G, Bellini M, Simoncini T. The female pelvic floor through midlife and aging. Maturitas 2013.**
- (21) **Hannestad YS, Rortveit G, Sandvik H, Hunskaar S. A community-based epidemiological survey of female urinary incontinence: the**

Norwegian EPINCONT study. Epidemiology of Incontinence in the County of Nord-Trondelag. J Clin Epidemiol 2000;53:1150-7.

- (22) Melville JL, Katon W, Delaney K, Newton K. Urinary incontinence in US women: a population-based study. Arch Intern Med 2005;165:537-42.**
- (23) Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21:167-78.**
- (24) Abrams P, Cardozo L, Khoury S, Wein A, (eds). International Consultation on Incontinence. 5th ed. Health Publication Ltd, Paris; 2013.**
- (25) Zhu L, Lang J, Liu C, Han S, Huang J, Li X. The epidemiological study of women with urinary incontinence and risk factors for stress urinary incontinence in China. Menopause 2009;16:831-6.**
- (26) Viktrup L, Rortveit G, Lose G. Risk of stress urinary incontinence twelve years after the first pregnancy and delivery. Obstet Gynecol 2006;108:248-54.**
- (27) Eason E, Labrecque M, Marcoux S, Mondor M. Effects of carrying a pregnancy and of method of delivery on urinary incontinence: a prospective cohort study. BMC Pregnancy Childbirth 2004;4:4.**
- (28) Rortveit G, Hannestad YS, Daltveit AK, Hunskaar S. Age- and type-dependent effects of parity on urinary incontinence: the Norwegian EPINCONT study. Obstet Gynecol 2001;98:1004-10.**
- (29) Delancey JO. Why do women have stress urinary incontinence? Neurourol Urodyn 2010;29 Suppl 1:S13-S17.**
- (30) Chen YC, Chen GD, Hu SW, Lin TL, Lin LY. Is the occurrence of storage and voiding dysfunction affected by menopausal transition or associated with the normal aging process? Menopause 2003;10:203-8.**
- (31) Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol 2006;50:1306-14.**

- (32) **Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int 2001;87:760-6.**
- (33) **Simeonova Z, Milsom I, Kullendorff AM, Molander U, Bengtsson C. The prevalence of urinary incontinence and its influence on the quality of life in women from an urban Swedish population. Acta Obstet Gynecol Scand 1999;78:546-51.**
- (34) **Altman D, Forsman M, Falconer C, Lichtenstein P. Genetic influence on stress urinary incontinence and pelvic organ prolapse. Eur Urol 2008;54:918-22.**
- (35) **Rohr G, Kragstrup J, Gaist D, Christensen K. Genetic and environmental influences on urinary incontinence: a Danish population-based twin study of middle-aged and elderly women. Acta Obstet Gynecol Scand 2004;83:978-82.**
- (36) **Hannestad YS, Lie RT, Rortveit G, Hunskaar S. Familial risk of urinary incontinence in women: population based cross sectional study. BMJ 2004;329:889-91.**
- (37) **Kelly HA, Dumm WM. Urinary incontinence in women, without manifest injury to the bladder. 1914. Int Urogynecol J Pelvic Floor Dysfunct 1998;9:158-64.**
- (38) **MARSHALL VF, MARCHETTI AA, KRANTZ KE. The correction of stress incontinence by simple vesicourethral suspension. Surg Gynecol Obstet 1949;88:509-18.**
- (39) **BURCH JC. Urethrovaginal fixation to Cooper's ligament for correction of stress incontinence, cystocele, and prolapse. Am J Obstet Gynecol 1961;81:281-90.**
- (40) **Stamey TA. Endoscopic suspension of the vesical neck for urinary incontinence. Surg Gynecol Obstet 1973;136:547-54.**
- (41) **Wennberg AL, Edlund C, Fall M, Pecker R. Stamey's abdominovaginal needle colposuspension for the correction of female genuine stress urinary incontinence--long-term results. Scand J Urol Nephrol 2003;37:419-23.**
- (42) **Chaikin DC, Rosenthal J, Blaivas JG. Pubovaginal fascial sling for all types of stress urinary incontinence: long-term analysis. J Urol 1998;160:1312-6.**

- (43) Breen JM, Geer BE, May GE. The fascia lata suburethral sling for treating recurrent urinary stress incontinence. Am J Obstet Gynecol 1997;177:1363-5.**
- (44) Simsiman AJ, Powell CR, Stratford RR, Menefee SA. Suburethral sling materials: best outcome with autologous tissue. Am J Obstet Gynecol 2005;193:2112-6.**
- (45) Hou JC, Lemack GE. The role of fascial slings in the treatment of stress urinary incontinence in women: a 2013 update. Curr Urol Rep 2013;14:247-52.**
- (46) Black NA, Downs SH. The effectiveness of surgery for stress incontinence in women: a systematic review. Br J Urol 1996;78:497-510.**
- (47) Kjolhede P. Long-term efficacy of Burch colposuspension: a 14-year follow-up study. Acta Obstet Gynecol Scand 2005;84:767-72.**
- (48) Petros PE, Ulmsten UI. An integral theory of female urinary incontinence. Experimental and clinical considerations. Acta Obstet Gynecol Scand Suppl 1990;153:7-31.**
- (49) Petros PE, Woodman PJ. The Integral Theory of continence. Int Urogynecol J Pelvic Floor Dysfunct 2008;19:35-40.**
- (50) Ulmsten U, Henriksson L, Johnson P, Varhos G. An ambulatory surgical procedure under local anesthesia for treatment of female urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 1996;7:81-5.**
- (51) Cox A, Herschorn S, Lee L. Surgical management of female SUI: is there a gold standard? Nat Rev Urol 2013;10:78-89.**
- (52) Kulseng-Hanssen S, Husby H, Schiotz HA. Follow-up of TVT operations in 1,113 women with mixed urinary incontinence at 7 and 38 months. Int Urogynecol J Pelvic Floor Dysfunct 2008;19:391-6.**
- (53) Rezapour M, Ulmsten U. Tension-Free vaginal tape (TVT) in women with mixed urinary incontinence--a long-term follow-up. Int Urogynecol J Pelvic Floor Dysfunct 2001;12 Suppl 2:S15-S18.**
- (54) Meschia M, Pifarotti P, Buonaguidi A, Gattei U, Spennacchio M. Tension-free vaginal tape (TVT) for treatment of stress urinary**

incontinence in women with low-pressure urethra. Eur J Obstet Gynecol Reprod Biol 2005;122:118-21.

- (55) Rezapour M, Falconer C, Ulmsten U. Tension-Free vaginal tape (TVT) in stress incontinent women with intrinsic sphincter deficiency (ISD)--a long-term follow-up. Int Urogynecol J Pelvic Floor Dysfunct 2001;12 Suppl 2:S12-S14.**
- (56) Bump RC, Mattiasson A, Bo K, Brubaker LP, Delancey JO, Klarskov P, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol 1996;175:10-7.**
- (57) Swift SE, Tate SB, Nicholas J. Correlation of symptoms with degree of pelvic organ support in a general population of women: what is pelvic organ prolapse? Am J Obstet Gynecol 2003;189:372-7.**
- (58) Samuelsson EC, Victor FT, Tibblin G, Svardsudd KF. Signs of genital prolapse in a Swedish population of women 20 to 59 years of age and possible related factors. Am J Obstet Gynecol 1999;180:299-305.**
- (59) Hendrix SL, Clark A, Nygaard I, Aragaki A, Barnabei V, McTiernan A. Pelvic organ prolapse in the Women's Health Initiative: gravity and gravidity. Am J Obstet Gynecol 2002;186:1160-6.**
- (60) Swift S, Woodman P, O'Boyle A, Kahn M, Valley M, Bland D, et al. Pelvic Organ Support Study (POSSST): the distribution, clinical definition, and epidemiologic condition of pelvic organ support defects. Am J Obstet Gynecol 2005;192:795-806.**
- (61) Rortveit G, Brown JS, Thom DH, Van Den Eeden SK, Creasman JM, Subak LL. Symptomatic pelvic organ prolapse: prevalence and risk factors in a population-based, racially diverse cohort. Obstet Gynecol 2007;109:1396-403.**
- (62) Brown JS, Waetjen LE, Subak LL, Thom DH, Van den Eeden S, Vittinghoff E. Pelvic organ prolapse surgery in the United States, 1997. Am J Obstet Gynecol 2002;186:712-6.**
- (63) Nygaard I, Barber MD, Burgio KL, Kenton K, Meikle S, Schaffer J, et al. Prevalence of symptomatic pelvic floor disorders in US women. JAMA 2008;300:1311-6.**

- (64) Smith FJ, Holman CD, Moorin RE, Tsokos N. Lifetime risk of undergoing surgery for pelvic organ prolapse. *Obstet Gynecol* 2010;116:1096-100.**
- (65) Shah AD, Kohli N, Rajan SS, Hoyte L. The age distribution, rates, and types of surgery for pelvic organ prolapse in the USA. *Int Urogynecol J Pelvic Floor Dysfunct* 2008;19:421-8.**
- (66) Gyhagen M, Bullarbo M, Nielsen TF, Milsom I. Prevalence and risk factors for pelvic organ prolapse 20 years after childbirth: a national cohort study in singleton primiparae after vaginal or caesarean delivery. *BJOG* 2013;120:152-60.**
- (67) Lukacz ES, Lawrence JM, Contreras R, Nager CW, Luber KM. Parity, mode of delivery, and pelvic floor disorders. *Obstet Gynecol* 2006;107:1253-60.**
- (68) Handa VL, Blomquist JL, Knoepp LR, Hoskey KA, McDermott KC, Munoz A. Pelvic floor disorders 5-10 years after vaginal or cesarean childbirth. *Obstet Gynecol* 2011;118:777-84.**
- (69) Moalli PA, Jones IS, Meyn LA, Zyczynski HM. Risk factors associated with pelvic floor disorders in women undergoing surgical repair. *Obstet Gynecol* 2003;101:869-74.**
- (70) Swift SE, Pound T, Dias JK. Case-control study of etiologic factors in the development of severe pelvic organ prolapse. *Int Urogynecol J Pelvic Floor Dysfunct* 2001;12:187-92.**
- (71) Jorgensen S, Hein HO, Gyntelberg F. Heavy lifting at work and risk of genital prolapse and herniated lumbar disc in assistant nurses. *Occup Med (Lond)* 1994;44:47-9.**
- (72) Woodman PJ, Swift SE, O'Boyle AL, Valley MT, Bland DR, Kahn MA, et al. Prevalence of severe pelvic organ prolapse in relation to job description and socioeconomic status: a multicenter cross-sectional study. *Int Urogynecol J Pelvic Floor Dysfunct* 2006;17:340-5.**
- (73) Chiaffarino F, Chatenoud L, Dindelli M, Meschia M, Buonaguidi A, Amicarelli F, et al. Reproductive factors, family history, occupation and risk of urogenital prolapse. *Eur J Obstet Gynecol Reprod Biol* 1999;82:63-7.**

- (74) Mant J, Painter R, Vessey M. Epidemiology of genital prolapse: observations from the Oxford Family Planning Association Study. Br J Obstet Gynaecol 1997;104:579-85.**
- (75) Altman D, Falconer C, Cnattingius S, Granath F. Pelvic organ prolapse surgery following hysterectomy on benign indications. Am J Obstet Gynecol 2008;198:572-6.**
- (76) Tegerstedt G, Miedel A, Maehle-Schmidt M, Nyren O, Hammarstrom M. Obstetric risk factors for symptomatic prolapse: a population-based approach. Am J Obstet Gynecol 2006;194:75-81.**
- (77) O'Boyle AL, Woodman PJ, O'Boyle JD, Davis GD, Swift SE. Pelvic organ support in nulliparous pregnant and nonpregnant women: a case control study. Am J Obstet Gynecol 2002;187:99-102.**
- (78) Sze EH, Sherard GB, III, Dolezal JM. Pregnancy, labor, delivery, and pelvic organ prolapse. Obstet Gynecol 2002;100:981-6.**
- (79) Barber MD, Visco AG, Wyman JF, Fantl JA, Bump RC. Sexual function in women with urinary incontinence and pelvic organ prolapse. Obstet Gynecol 2002;99:281-9.**
- (80) Boyles SH, Weber AM, Meyn L. Procedures for pelvic organ prolapse in the United States, 1979-1997. Am J Obstet Gynecol 2003;188:108-15.**
- (81) Haessler AL, Lin LL, Ho MH, Betson LH, Bhatia NN. Reevaluating occult incontinence. Curr Opin Obstet Gynecol 2005;17:535-40.**
- (82) Fatton B. Is there any evidence to advocate SUI prevention in continent women undergoing prolapse repair? An overview. Int Urogynecol J Pelvic Floor Dysfunct 2009;20:235-45.**
- (83) Gregorio G, Hillemanns HG. Urethral closure function in women with prolapse. International Urogynecology Journal 1990;1:143-5.**
- (84) Richardson DA, Bent AE, Ostergard DR. The effect of uterovaginal prolapse on urethrovesical pressure dynamics. Am J Obstet Gynecol 1983;146:901-5.**
- (85) Long CY, Hsu SC, Wu TP, Sun DJ, Su JH, Tsai EM. Urodynamic comparison of continent and incontinent women with severe uterovaginal prolapse. J Reprod Med 2004;49:33-7.**

- (86) Bump RC, Fantl JA, Hurt WG. The mechanism of urinary continence in women with severe uterovaginal prolapse: results of barrier studies. *Obstet Gynecol* 1988;72:291-5.**
- (87) Bump RC, Hurt WG, Theofrastous JP, Addison WA, Fantl JA, Wyman JF, et al. Randomized prospective comparison of needle colposuspension versus endopelvic fascia plication for potential stress incontinence prophylaxis in women undergoing vaginal reconstruction for stage III or IV pelvic organ prolapse. The Continence Program for Women Research Group. *Am J Obstet Gynecol* 1996;175:326-33.**
- (88) Visco AG, Brubaker L, Nygaard I, Richter HE, Cundiff G, Fine P, et al. The role of preoperative urodynamic testing in stress-continent women undergoing sacrocolpopexy: the Colpopexy and Urinary Reduction Efforts (CARE) randomized surgical trial. *Int Urogynecol J Pelvic Floor Dysfunct* 2008;19:607-14.**
- (89) Ellstrom Engh AM, Ekeryd A, Magnusson A, Olsson I, Otterlind L, Tobiasson G. Can de novo stress incontinence after anterior wall repair be predicted? *Acta Obstet Gynecol Scand* 2011;90:488-93.**
- (90) Svenningsen R, Borstad E, Spydsaug AE, Sandvik L, Staff AC. Occult incontinence as predictor for postoperative stress urinary incontinence following pelvic organ prolapse surgery. *Int Urogynecol J* 2012;23:843-9.**
- (91) Malak M. The role of anti-incontinence surgery in management of occult urinary stress incontinence. *Int Urogynecol J* 2012;23:823-5.**
- (92) Bergman A, Koonings PP, Ballard CA. Predicting postoperative urinary incontinence development in women undergoing operation for genitourinary prolapse. *Am J Obstet Gynecol* 1988;158:1171-5.**
- (93) Ghoniem GM, Walters F, Lewis V. The value of the vaginal pack test in large cystoceles. *J Urol* 1994;152:931-4.**
- (94) Gordon D, Groutz A, Wolman I, Lessing JB, David MP. Development of postoperative urinary stress incontinence in clinically continent patients undergoing prophylactic Kelly plication during genitourinary prolapse repair. *Neurourol Urodyn* 1999;18:193-7.**
- (95) Groutz A, Gold R, Pauzner D, Lessing JB, Gordon D. Tension-free vaginal tape (TVT) for the treatment of occult stress urinary**

incontinence in women undergoing prolapse repair: a prospective study of 100 consecutive cases. *Neurourol Urodyn* 2004;23:632-5.

- (96) Klutke JJ, Ramos S. Urodynamic outcome after surgery for severe prolapse and potential stress incontinence. *Am J Obstet Gynecol* 2000;182:1378-81.**
- (97) Liang CC, Chang YL, Chang SD, Lo TS, Soong YK. Pessary test to predict postoperative urinary incontinence in women undergoing hysterectomy for prolapse. *Obstet Gynecol* 2004;104:795-800.**
- (98) Reena C, Kekre AN, Kekre N. Occult stress incontinence in women with pelvic organ prolapse. *Int J Gynaecol Obstet* 2007;97:31-4.**
- (99) Rosenzweig BA, Pushkin S, Blumenfeld D, Bhatia NN. Prevalence of abnormal urodynamic test results in continent women with severe genitourinary prolapse. *Obstet Gynecol* 1992;79:539-42.**
- (100) Versi E, Lyell DJ, Griffiths DJ. Videourodynamic diagnosis of occult genuine stress incontinence in patients with anterior vaginal wall relaxation. *J Soc Gynecol Investig* 1998;5:327-30.**
- (101) Wei JT, Nygaard I, Richter HE, Nager CW, Barber MD, Kenton K, et al. A midurethral sling to reduce incontinence after vaginal prolapse repair. *N Engl J Med* 2012;366:2358-67.**
- (102) Meschia M, Pifarotti P, Spennacchio M, Buonaguidi A, Gattei U, Somigliana E. A randomized comparison of tension-free vaginal tape and endopelvic fascia plication in women with genital prolapse and occult stress urinary incontinence. *Am J Obstet Gynecol* 2004;190:609-13.**
- (103) Maher C, Feiner B, Baessler K, Schmid C. Surgical management of pelvic organ prolapse in women 2013. *Cochrane Database Syst Rev* 2013;4:CD004014.**
- (104) Borstad E, Rud T. The risk of developing urinary stress-incontinence after vaginal repair in continent women. A clinical and urodynamic follow-up study. *Acta Obstet Gynecol Scand* 1989;68:545-9.**
- (105) Brubaker L, Cundiff GW, Fine P, Nygaard I, Richter HE, Visco AG, et al. Abdominal sacrocolpopexy with Burch colposuspension to reduce urinary stress incontinence. *N Engl J Med* 2006;354:1557-66.**

- (106) Altman D, Vayrynen T, Engh ME, Axelsen S, Falconer C. Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. N Engl J Med 2011;364:1826-36.**
- (107) Hiltunen R, Nieminen K, Takala T, Heiskanen E, Merikari M, Niemi K, et al. Low-weight polypropylene mesh for anterior vaginal wall prolapse: a randomized controlled trial. Obstet Gynecol 2007;110:455-62.**
- (108) Ballert KN, Biggs GY, Isenalumhe A, Jr., Rosenblum N, Nitti VW. Managing the urethra at transvaginal pelvic organ prolapse repair: a urodynamic approach. J Urol 2009;181:679-84.**
- (109) Schraffordt Koops SE, Bisseling TM, Heintz AP, Vervest HA. Prospective analysis of complications of tension-free vaginal tape from The Netherlands Tension-free Vaginal Tape study. Am J Obstet Gynecol 2005;193:45-52.**
- (110) Dwyer PL. Women with occult stress incontinence should not routinely have a mid-urethral sling with prolapse surgery. Int Urogynecol J 2012;23:827-9.**
- (111) Ennemoser S, Schonfeld M, von B, V, Dian D, Friese K, Jundt K. Clinical relevance of occult stress urinary incontinence (OSUI) following vaginal prolapse surgery: long-term follow-up. Int Urogynecol J 2012;23:851-5.**
- (112) Chermansky CJ, Krlin RM, Winters JC. Selective management of the urethra at time of pelvic organ prolapse repair: an assessment of postoperative incontinence and patient satisfaction. J Urol 2012;187:2144-8.**
- (113) Chaikin DC, Groutz A, Blaivas JG. Predicting the need for anti-incontinence surgery in continent women undergoing repair of severe urogenital prolapse. J Urol 2000;163:531-4.**
- (114) Kulseng-Hanssen S. The development of a national database of the results of surgery for urinary incontinence in women. BJOG 2003;110:975-82.**
- (115) Kulseng-Hanssen S, Borstad E. The development of a questionnaire to measure the severity of symptoms and the quality of life before and after surgery for stress incontinence. BJOG 2003;110:983-8.**

- (116) Berild GH, Kulseng-Hanssen S. Reproducibility of a cough and jump stress test for the evaluation of urinary incontinence. *Int Urogynecol J* 2012;23:1449-53.
- (117) Swift SE, Yoon EA. Test-retest reliability of the cough stress test in the evaluation of urinary incontinence. *Obstet Gynecol* 1999;94:99-102.
- (118) Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *Clin Chem Lab Med* 2003;41:68-73.
- (119) Centre for evidence based medicine, Toronto Canada. 2013 [cited 2013 Sep 20]; Available from: URL: <http://ktclearinghouse.ca/cebm/toolbox/statscale>
- (120) Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects as adopted by the 59th WMA General Assembly, Seoul, October 2008. 2008 [cited 2013 Sep 20]; Available from: URL: <http://www.wma.net/en/30publications/10policies/b3/>
- (121) Clemons JL, LaSala CA. The tension-free vaginal tape in women with a non-hypermobility urethra and low maximum urethral closure pressure. *Int Urogynecol J Pelvic Floor Dysfunct* 2007;18:727-32.
- (122) Ankardal M, Heiwall B, Lausten-Thomsen N, Cernelid J, Milsom I. Short- and long-term results of the tension-free vaginal tape procedure in the treatment of female urinary incontinence. *Acta Obstet Gynecol Scand* 2006;85:986-92.
- (123) Holmgren C, Nilsson S, Lanner L, Hellberg D. Long-term results with tension-free vaginal tape on mixed and stress urinary incontinence. *Obstet Gynecol* 2005;106:38-43.
- (124) Houwert RM, Venema PL, Aquarius AE, Bruinse HW, Roovers JP, Vervest HA. Risk factors for failure of retropubic and transobturator midurethral slings. *Am J Obstet Gynecol* 2009;201:202-8.
- (125) Uebersax JS, Wyman JF, Shumaker SA, McClish DK, Fantl JA. Short forms to assess life quality and symptom distress for urinary incontinence in women: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program for Women Research Group. *Neurourol Urodyn* 1995;14:131-9.

- (126) Stach-Lempinen B, Kujansuu E, Laippala P, Metsanoja R. Visual analogue scale, urinary incontinence severity score and 15 D-- psychometric testing of three different health-related quality-of-life instruments for urinary incontinent women. *Scand J Urol Nephrol* 2001;35:476-83.
- (127) Barber MD, Kuchibhatla MN, Pieper CF, Bump RC. Psychometric evaluation of 2 comprehensive condition-specific quality of life instruments for women with pelvic floor disorders. *Am J Obstet Gynecol* 2001;185:1388-95.
- (128) Clemons JL, Aguilar VC, Tillinghast TA, Jackson ND, Myers DL. Patient satisfaction and changes in prolapse and urinary symptoms in women who were fitted successfully with a pessary for pelvic organ prolapse. *Am J Obstet Gynecol* 2004;190:1025-9.
- (129) Ammendrup AC, Jorgensen A, Sander P, Ottesen B, Lose G. A Danish national survey of women operated with mid-urethral slings in 2001. *Acta Obstet Gynecol Scand* 2009;88:1227-33.
- (130) Koops SE, Bisseling TM, van Brummen HJ, Heintz AP, Vervest HA. What determines a successful tension-free vaginal tape? A prospective multicenter cohort study: results from The Netherlands TVT database. *Am J Obstet Gynecol* 2006;194:65-74.
- (131) Guldberg R, Brostrom S, Hansen JK, Kaerlev L, Gradel KO, Norgard BM, et al. The Danish Urogynaecological Database: establishment, completeness and validity. *Int Urogynecol J* 2013;24:983-90.
- (132) Lovatsis D, Gupta C, Dean E, Lee F. Tension-free vaginal tape procedure is an ideal treatment for obese patients. *Am J Obstet Gynecol* 2003;189:1601-4.
- (133) Mukherjee K, Constantine G. Urinary stress incontinence in obese women: tension-free vaginal tape is the answer. *BJU Int* 2001;88:881-3.
- (134) Rafii A, Darai E, Haab F, Samain E, Levardon M, Deval B. Body mass index and outcome of tension-free vaginal tape. *Eur Urol* 2003;43:288-92.
- (135) Hellberg D, Holmgren C, Lanner L, Nilsson S. The very obese woman and the very old woman: tension-free vaginal tape for the

treatment of stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2007;18:423-9.

- (136) Hannestad YS, Rortveit G, Daltveit AK, Hunskaar S. Are smoking and other lifestyle factors associated with female urinary incontinence? The Norwegian EPINCONT Study. BJOG 2003;110:247-54.**
- (137) Blumel JE, Castelo-Branco C, Rocangliolo ME, Bifa L, Tacla X, Mamani L. Changes in body mass index around menopause: a population study of Chilean woman. Menopause 2001;8:239-44.**
- (138) Al-Mandeel H, Ross S, Robert M, Milne J. Incidence of stress urinary incontinence following vaginal repair of pelvic organ prolapse in objectively continent women. Neurourol Urodyn 2011;30:390-4.**
- (139) Schierlitz L, Dwyer PL, Rosamilia A, De SA, Murray C, Thomas E, et al. Pelvic organ prolapse surgery with and without tension-free vaginal tape in women with occult or asymptomatic urodynamic stress incontinence: a randomised controlled trial. Int Urogynecol J 2013.**
- (140) Brubaker L, Nygaard I, Richter HE, Visco A, Weber AM, Cundiff GW, et al. Two-year outcomes after sacrocolpopexy with and without burch to prevent stress urinary incontinence. Obstet Gynecol 2008;112:49-55.**
- (141) Myers DL, LaSala CA, Hogan JW, Rosenblatt PL. The effect of posterior wall support defects on urodynamic indices in stress urinary incontinence. Obstet Gynecol 1998;91:710-4.**
- (142) Oversand SH, Staff AC, Spydsaug AE, Svenningsen R, Borstad E. Long-term follow-up after native tissue repair for pelvic organ prolapse. Int Urogynecol J 2013.**
- (143) Nilsson CG, Palva K, Rezapour M, Falconer C. Eleven years prospective follow-up of the tension-free vaginal tape procedure for treatment of stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2008;19:1043-7.**
- (144) Olsson I, Abrahamsson AK, Kroon UB. Long-term efficacy of the tension-free vaginal tape procedure for the treatment of urinary incontinence: a retrospective follow-up 11.5 years post-operatively. Int Urogynecol J Pelvic Floor Dysfunct 2010;21:679-83.**

- (145) Serati M, Ghezzi F, Cattoni E, Braga A, Siesto G, Torella M, et al. Tension-free vaginal tape for the treatment of urodynamic stress incontinence: efficacy and adverse effects at 10-year follow-up. *Eur Urol* 2012;61:939-46.
- (146) Heinonen P, Ala-Nissila S, Kiilholma P, Laurikainen E. Tension-free vaginal tape procedure without preoperative urodynamic examination: Long-term outcome. *Int J Urol* 2012;19:1003-9.
- (147) Groutz A, Rosen G, Cohen A, Gold R, Lessing JB, Gordon D. Ten-year subjective outcome results of the retropubic tension-free vaginal tape for treatment of stress urinary incontinence. *J Minim Invasive Gynecol* 2011;18:726-9.
- (148) Oh SJ, Ku JH, Hong SK, Kim SW, Paick JS, Son H. Factors influencing self-perceived disease severity in women with stress urinary incontinence combined with or without urge incontinence. *Neurourol Urodyn* 2005;24:341-7.
- (149) Nilsson CG, Palva K, Aarnio R, Morcos E, Falconer C. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. *Int Urogynecol J* 2013;24:1265-9.
- (150) Jonsson FM, Siddiqui NY, Kawasaki A, Wu JM. Long-term outcomes after stress urinary incontinence surgery. *Obstet Gynecol* 2012;120:83-90.
- (151) Neuman M. Low incidence of post-TVT genital prolapse. *Int Urogynecol J Pelvic Floor Dysfunct* 2003;14:191-2.
- (152) Ward KL, Hilton P. Tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence: 5-year follow up. *BJOG* 2008;115:226-33.
- (153) Dietz HP, Wilson PD. Colposuspension success and failure: a long-term objective follow-up study. *Int Urogynecol J Pelvic Floor Dysfunct* 2000;11:346-51.
- (154) Kjolhede P, Noren B, Ryden G. Prediction of genital prolapse after Burch colposuspension. *Acta Obstet Gynecol Scand* 1996;75:849-54.
- (155) Saaby ML, Lose G. Repeatability of post-void residual urine ≥ 100 ml in urogynaecologic patients. *Int Urogynecol J* 2012;23:207-9.

- (156) Holmgren C, Nilsson S, Lanner L, Hellberg D. Frequency of de novo urgency in 463 women who had undergone the tension-free vaginal tape (TVT) procedure for genuine stress urinary incontinence--a long-term follow-up. *Eur J Obstet Gynecol Reprod Biol* 2007;132:121-5.
- (157) Cammu H, Van Den Abbeele E, Nagel H, Haentjens P. Factors predictive of outcome in tension-free vaginal tape procedure for urinary stress incontinence in a teaching hospital. *Int Urogynecol J Pelvic Floor Dysfunct* 2009;20:775-80.
- (158) McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. *Maturitas* 1992;14:103-15.
- (159) Falconer C, Ekman-Ordeberg G, Ulmsten U, Westergren-Thorsson G, Barchan K, Malmstrom A. Changes in paraurethral connective tissue at menopause are counteracted by estrogen. *Maturitas* 1996;24:197-204.
- (160) Phillips SK, Rook KM, Siddle NC, Bruce SA, Woledge RC. Muscle weakness in women occurs at an earlier age than in men, but strength is preserved by hormone replacement therapy. *Clin Sci (Lond)* 1993;84:95-8.
- (161) de Groat WC, Fraser MO, Yoshiyama M, Smerin S, Tai C, Chancellor MB, et al. Neural control of the urethra. *Scand J Urol Nephrol Suppl* 2001;35-43.
- (162) Lee KS, Choo MS, Doo CK, Han DH, Lee YS, Kim JY, et al. The long term (5-years) objective TVT success rate does not depend on predictive factors at multivariate analysis: a multicentre retrospective study. *Eur Urol* 2008;53:176-82.
- (163) Song PH, Kim YD, Kim HT, Lim HS, Hyun CH, Seo JH, et al. The 7-year outcome of the tension-free vaginal tape procedure for treating female stress urinary incontinence. *BJU Int* 2009;104:1113-7.
- (164) Rardin CR, Kohli N, Rosenblatt PL, Miklos JR, Moore R, Strohsmittter WC. Tension-free vaginal tape: outcomes among women with primary versus recurrent stress urinary incontinence. *Obstet Gynecol* 2002;100:893-7.

- (165) Parden AM, Gleason JL, Jauk V, Garner R, Ballard A, Richter HE. Incontinence outcomes in women undergoing primary and repeat midurethral sling procedures. Obstet Gynecol 2013;121:273-8.**
- (166) Pang MW, Chan LW, Yip SK. One-year urodynamic outcome and quality of life in patients with concomitant tension-free vaginal tape during pelvic floor reconstruction surgery for genitourinary prolapse and urodynamic stress incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2003;14:256-60.**
- (167) Pepe MS, Janes H, Longton G, Leisenring W, Newcomb P. Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. Am J Epidemiol 2004;159:882-90.**
- (168) Borstad E, Abdelnoor M, Staff AC, Kulseng-Hanssen S. Surgical strategies for women with pelvic organ prolapse and urinary stress incontinence. Int Urogynecol J 2010;21:179-86.**
- (169) Kleeman S, Vassallo B, Segal J, Hungler M, Karram M. The ability of history and a negative cough stress test to detect occult stress incontinence in patients undergoing surgical repair of advanced pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct 2006;17:27-9.**
- (170) Jundt K, Wagner S, von B, V, Friese K, Peschers UM. Occult incontinence in women with pelvic organ prolapse - Does it matter? Eur J Med Res 2010;15:112-6.**

11. APPENDICES

Appendix 1

The Norwegian Female Incontinence Registry (NFIR) urinary incontinence questionnaire (English version).

Sigurd Kulseng-Hanssen has translated the NFIR urinary incontinence questionnaire below to English version. It has not been retranslated to Norwegian.

Norwegian UroGynaecological Group, (NUGG) urinary incontinence questionnaire .

Hospital id.

Patent id.

Date

Age

Please answer all the questions. Mark by use of dark blue or black marker pen or ballpoint pen. Don't fold the paper.

(Mark yes, no or not relevant for each alternative in question 1.)

	<i>yes</i>	<i>no</i>	<i>not relevant</i>
1. Do you leak urine?			
when you cough	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
when you sneeze	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
when you laugh	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
when you walk up or down in stairs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
when you raise from bed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
when you lift heavy objects	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
during physical activity (running to the catch the bus)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
during sports	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
during intercourse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

(Mark one alternative for each question from 2 to 6)

2. How often do you leak urine in relation to physical activity, when you laugh, cough or sneeze?

- ☐ never
- ☐ 1 – 4 times each month
- ☐ 1 – 6 times each week
- ☐ once per day
- ☐ more than once per day

3. How large is the amount of urine you usually leak during physical activity or when you laugh, cough or sneeze?

- ☐ nothing
- ☐ drops / moist underwear
- ☐ dripping / wet underwear
- ☐ running / passes through all you clothes,
- ☐ running down your legs or down at the floor

4. How often do you experience sudden and imperious need to void and urinary leakage before you reach the toilet?

- ☐ never
- ☐ 1 – 4 times per month
- ☐ 1 – 6 times per week
- ☐ once per day
- ☐ more than once per day

5. How large is the amount of urine you usually leak when you experience sudden and imperious need to void and urinary leakage

- ☐ nothing
- ☐ drops / moist underwear
- ☐ dripping / wet underwear
- ☐ running / passes through all you clothes,
- ☐ running down your legs or down at the floor

6. If you experience symptoms both as those described in question 2 and question 4, what is troubling you the most?

- ☐ leakage during physical activities more than leakage related to urge
- ☐ leakage during urge more than leakage during physical activity
- ☐ equally trouble by leakage during urge as by leakage during physical activity.
- ☐ I don't have leakage as described in question 2 nor in question 4.

(Mark only one alternative for each question 7 – 11)

7. How many incontinence pads do you use?

- ☐ none
- ☐ 1 – 3 per week
- ☐ 4 – 6 per week
- ☐ 1 – 4 per day
- ☐ more than 4 per day

8. **How many times have you been treated for cystitis the last 6 months**
☐ never ☐ once ☐ 2 – 3 times ☐ 4 times ☐ more than 4 times
9. **How often do you avoid activities (for example a hobby, physical training or going out) because you are afraid of leaking urine?**
☐ never ☐ seldom ☐ sometimes ☐ often ☐ always
10. **Do you avoid places and situations where you are aware of that a toilet is not easily available?**
☐ never ☐ seldom ☐ sometimes ☐ often ☐ always
11. **Is your sexual life influenced by your leakage problem? (To be answered before treatment.)**
☐ not relevant
☐ substantially improved ☐ some improvement ☐ unchanged ☐ some deterioration ☐ substantial deterioration
- Mark yes, no or not relevant for each question under 12*
12. **Does your urinary leakage influence**
- | | yes | no | not relevant |
|--|--------------------------|--------------------------|--------------------------|
| your vacation? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| your family life? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| your social life (going out, meeting friends)? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| your sleep? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
- (Mark only one alternative for each question 13 – 14)*
13. **Is your sexual life influenced by your leakage problem? (To be answered after treatment.)**
☐ not relevant
☐ substantially improved ☐ some improvement ☐ unchanged ☐ some deterioration ☐ substantial deterioration
14. **Are you satisfied with the result of the treatment you have received in order to cure your urinary leakage?**
☐ Very satisfied ☐ moderately satisfied ☐ neither satisfied nor unsatisfied ☐ moderately unsatisfied ☐ very unsatisfied

Information given in this questionnaire, will be reported to "The Register for Incontinence", a national data base for assurance of quality. Your name and identification number is not transferred. Your identity is known exclusively by your treating physician. © S. Kulseng-Hanssen

Please do not fill in. Will be filled in by a physician.

<input type="text"/>	<input type="text"/>	<input type="text"/>	Date of incontinence surgery	Mean. voiding volume ml.	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	Number of months after the operation		Leakage during 24 hours pad test gr.	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	Number of voidings per 24 hours		Leakage during stress test gr	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	Surgeon id. number		<input type="text"/>	Number of earlier surgical procedures to cure incontinence	Residual urine ml.	<input type="text"/>	<input type="text"/>
Surgical procedure <input type="checkbox"/> open Burch <input type="checkbox"/> lapsc. Burch <input type="checkbox"/> MMK <input type="checkbox"/> TVT <input type="checkbox"/> Stamey							
<input type="checkbox"/> Kelly <input type="checkbox"/> sling <input type="checkbox"/> other IVS <input type="checkbox"/> perineal injection <input type="checkbox"/> obturator							
The incontinence surgical procedure was combined with a surgical procedure to cure vaginal prolaps yes <input type="checkbox"/>							
Date for cutting of sling							
Complications none <input type="checkbox"/> bladder perforation <input type="checkbox"/> haematoma <input type="checkbox"/> superficial wound infection <input type="checkbox"/>							
deep wound infection <input type="checkbox"/> catheter > week <input type="checkbox"/> catheter > 1 month <input type="checkbox"/> other complications <input type="checkbox"/>							

Appendix 2

The Norwegian Female Incontinence Registry (NFIR) urinary incontinence questionnaire (Norwegian version).

Pre og peroperativ registrering

Dato for innfylling av skjemaet

		.			.		
--	--	---	--	--	---	--	--

pasientnummer

--	--	--	--	--

Vær vennlig **besvar alle spørsmål**. De opplysninger som avgis på dette spørreskjema, vil bli rapportert til Norsk kvinnelig inkontinensregister. Navn og personnummer overføres ikke. Kun din behandlende lege kjenner din identitet

(Kryss av **ja, nei, eller ikke aktuelt for alle alternativer** i spørsmål 1)

1. Lekker du urin?

- | | | | |
|--|-----------------------------|------------------------------|---------------------------------------|
| når du hoster | <input type="checkbox"/> Ja | <input type="checkbox"/> Nei | |
| når du nyser | <input type="checkbox"/> Ja | <input type="checkbox"/> Nei | |
| når du ler | <input type="checkbox"/> Ja | <input type="checkbox"/> Nei | |
| når du går i trapper | <input type="checkbox"/> Ja | <input type="checkbox"/> Nei | |
| når du står opp av sengen | <input type="checkbox"/> Ja | <input type="checkbox"/> Nei | |
| når du løfter tungt (tunge bæreposer) | <input type="checkbox"/> Ja | <input type="checkbox"/> Nei | <input type="checkbox"/> Ikke aktuelt |
| ved fysisk aktivitet (løper for å nå bussen) | <input type="checkbox"/> Ja | <input type="checkbox"/> Nei | <input type="checkbox"/> Ikke aktuelt |
| ved sportsaktiviteter | <input type="checkbox"/> Ja | <input type="checkbox"/> Nei | <input type="checkbox"/> Ikke aktuelt |
| ved samleie | <input type="checkbox"/> Ja | <input type="checkbox"/> Nei | <input type="checkbox"/> Ikke aktuelt |

(Kryss av **et alternativ for hvert av spørsmålene 2 - 6**)

2. Hvor ofte lekker du urin i forbindelse med fysisk aktivitet, når du ler, hoster eller nyser?

- ☐ aldri
- ☐ 1-4 ganger per måned
- ☐ 1-6 ganger per uke
- ☐ 1 gang per dag
- ☐ mer enn 1 gang per dag

3. Hvor stor mengde urin lekker du vanligvis ved fysisk aktivitet, når du ler, hoster eller nyser?

- ☐ ingen
- ☐ dråper/fuktig undertøy
- ☐ drypper/vått undertøy
- ☐ renner/går gjennom ytterklær
- ☐ renner nedover bena eller ned på gulvet

4. Hvor ofte opplever du plutselig sterk trang til å late vannet og lekker urin før du når frem til toalettet?

- ☐ aldri
- ☐ 1-4 ganger per måned
- ☐ 1-6 ganger per uke
- ☐ 1 gang per dag
- ☐ mer enn 1 gang per dag

5. Hvor stor mengde urin lekker du vanligvis når du har trang til å late vannet og lekker urin før du når frem til toalettet?

- ☐ ingen
- ☐ dråper/fuktig undertøy
- ☐ drypper/vått undertøy
- ☐ renner/går gjennom ytterklær
- ☐ renner nedover bena eller ned på gulvet

6. Dersom du har symptomer både som i spørsmål 2 og spørsmål 4, hva er du mest plaget av?

- ☐ lekkasje ved fysisk aktivitet mer enn lekkasje ved trang
- ☐ lekkasje ved trang mer enn ved lekkasje ved fysisk aktivitet
- ☐ like mye plaget av lekkasje ved trang som ved lekkasje ved fysisk aktivitet
- ☐ har ikke lekkasje hverken som under spørsmål 2 eller spørsmål 4

Draft



